MEASURING PMTCT EFFECTIVENSS THROUGH HIV FREE SURVIVAL IN CHILDREN UNDER 2 YEARS

Sineke Tembeka

Supervisor: Professor David Coetzee

Snktem002

PREAMBLE

Declaration

I, Tembeka Sineke (SNKTEM002), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature Signed by candidate

Signature removed

Date 21 July 2015

Acknowledgements

I would like to send a big thank you to my supervisor Professor David Coetzee for coming up with the topic for my dissertation, reading through several drafts and giving his expert and supporting me throughout the process of writing this dissertation. Without his constructive feedback and input, I would not have completed on time.

Thank you to Dr Kathryn Stinson, for advising on some of the analysis and continuous encouragement.

Final thank you to God Almighty, and to my family and friends for all the support.

Dissertation Abstract

Background: The prevalence of HIV was greater than 30% in the Free State province in South Africa and PMTCT services were widely available at the time the guidelines recommended nevirapine in labour and to the child postpartum.

Aim: The aim was to determine the effectiveness of the PMTCT program in the Free State by measuring HIV transmission and HIV-free survival in children less than two years of age. Variables associated with HIV transmission and HIV-free survival including PMTCT uptake by mother, demographic characteristics, type of delivery and breastfeeding status were investigated.

Methods: This was a secondary analysis of data collected from a cross sectional community household survey, using multistage cluster sampling. The population was all women who had given birth to a child in the two years prior to the study in the catchment area of three sub-districts that were randomly selected in Free State. All mothers were anonymously tested for HIV and if infected the child was also tested. Trained field workers interviewed mothers, identified children who had died and collected data on variables that could be related to transmission and survival. Logistic regression was used to determine risk factors.

Results: HIV exposure and outcome status was known for 874 (75.50%) of the 1158 children under 2 years of age who were identified. Ninety seven children (11.10%) were exposed to HIV. One exposed (1.03%) and HIV positive child died from an HIV related illness. One other exposed but uninfected child (1.03%) died from other causes. Thirty (3.86%) unexposed children died. Transmission was 52.63% from mothers who did not

receive any form of PMTCT and 11.84% in mothers who received some form of PMTCT. There was a 72% reduction in survival in children who had been hospitalised at least once since birth while those who were still breastfed at the time of the interview were 5.08 times more likely to survive (p=0.001). Although many studies have shown that a number of factors are associated with HIV transmission from mother to child, in this study no variables were significantly associated with transmission in the adjusted multivariate analysis, besides a child being hospitalized at least once since birth (p<0.001).

Conclusion: Breast feeding and being admitted to hospital at least once since birth were significantly associated with survival and further research is recommended on the impact of these factors on transmission and survival. .

Table of Contents

List of figures

Protocol

Literature review

Journal manuscript

List of abbreviations

AIDS Acquired Immune Deficiency Syndrome

ARV Antiretroviral

ANC Antenatal care

BF Breast Feeding

CD4 The absolute CD4 cell count measures the number of CD4-T-cells in each count cubic ml of blood

CDC Centres of Disease Control and Prevention, Atlanta, United States of America

HAART Highly Active Anti-Retroviral Therapy

HIV Human Immunodeficiency Virus

MTCT Mother to Child Transmission of HIV

NVP Nevirapine

SD NVP Single dose-Nevirapine

PCR Polymerase Chain Reaction

PMTCT Prevention of Mother to Child Transmission of HIV

RCT Randomised Control Trial

UNAIDS The Joint United Nations Program on HIV/AIDS

WHO World Health Organization

ZDV Zidovudine

PART A

THESIS PROTOCOL

Measuring PMTCT effectiveness through HIV free survival in children under 2 years

Protocol summary

Evaluation of the operational effectiveness of large scale national programs for the prevention of mother to child transmission (PMTCT) of human immune virus (HIV) in sub-Saharan Africa remains limited.

Primary objective

The primary objective will be to measure the effectiveness of program for the PMTCT of HIV in 3 sub-districts in the Free State province by measuring HIV-free survival in children under the age of 2 years, using data collected as part of a larger three country study from October 2008 till May 2009.

Methods

This study will be a secondary analysis of data collected from a cross sectional community household survey, using multistage cluster sampling. The catchment area for each of the facilities where infants were delivered was mapped and divided into clusters. A sample of clusters was selected and within each cluster, a random sample of households was visited. If there was a child born in the previous 2 years in the household, the mother-child pair was eligible for the study. Logistic regression will be used to determine risk factors associated with HIV transmission and survival.

Ethics

Mothers or guardians provided informed consent to take part in the study.

Introduction

Background

HIV/AIDS remains a major public health issue with 1.6 million people having died of AIDS-related illnesses worldwide in 2012 alone (1). The majority of all infections (69%) were in sub-Saharan Africa (2). In South Africa 200,000 deaths in 2013 were due to HIV/AIDS and 6,300,000 people were living with HIV and the majority of infections were among women (3).

HIV can be transmitted from an HIV-infected woman to her child and this is called mother to child transmission (MTCT) during pregnancy, labour and delivery and breastfeeding. MTCT of HIV is also known as vertical transmission. The overall HIV prevalence among women attending antenatal health care centres was 29.5% (95% CI: 28.8 to 30.2%) in 2012. Mother to child transmission of HIV is more likely in women, from poorer backgrounds, with less education, who did not receive any form of PMTCT, who did not exclusively breast feed or exclusively provide replacement feeding and who were unemployed. Studies show that interventions where the mother received HAART and where the child received ARV prophylaxis have the greatest impact on HIV transmission and HIV-free survival (4-7).

HIV transmission from mother to child is also more likely to occur in younger women. This could be due to the fact that younger women were infected with HIV more recently and therefore had higher HIV viral loads (8-11). Socio-economic status is associated with vertical transmission, but this maybe because it is associated with unemployment,

a lower level of education or a combination of variables that impact on socio-economic status.

Prior to the advent of the HIV epidemic, many studies showed that children who were exclusively breast fed for the first six months of life were more likely to survive than children who received replacement feeding or mixed feeding. They were less likely to have diarrhoea, lower respiratory infections and otitis media. Initially children of HIV-infected mothers were advised to receive replacement feeding, as HIV transmission was more likely to occur through breast feeding. Recent studies show that mothers who are receiving HAART are unlikely to transmit HIV through breast feeding and thus exclusive breast feeding is promoted in resource-limited settings, because of the risk of co-morbidities in children who are not breast fed.

Rapid implementation of PMTCT interventions in many countries, including South Africa, has led to a substantial reduction in the number of children infected perinatally. The reduction in infant mortality as a result of HIV is a result of effective HIV programs and increased survival of infected mothers (12). The dramatic decline in perinatal HIV infection has been most prominent in the resource rich countries such as the United States of America (13). In the first national survey of the PMTCT program in South Africa in 2010, the overall transmission rate from mother to child was 3.5% and in 2014 the rate was 2.7% (14).

PMTCT effectiveness

Assessment of the effectiveness of PMTCT programs encompasses the evaluation of the long-term aggregate effect of programs over a period of time, such as a change in

incidence of HIV and AIDS-related morbidity and mortality. “Effectiveness is described as the prophylactic benefit of a PMTCT intervention when implemented in everyday practice” (15). It is the function of how much the antiretroviral therapy reduces the risk of MTCT or efficacy and the proportion of the intended population at risk that accesses and uses the intervention correctly or coverage. The most common measurement of PMTCT effectiveness is the evaluation of coverage only.

PMTCT services in Free State Province

Free State is one of the provinces with the highest burden of HIV in South Africa. In 2012 Free State had the third highest prevalence of HIV at 32.0% (95%CI 29.8 to 34.3%) among women attending antenatal services in the public sector followed by KwaZulu-Natal and Mpumalanga (16). In 2001 eighteen sites were set up by the national HIV/AIDS Directorate as pilot PMTCT programs and lessons learned from these pilot sites were then transferred to a wider program. Free State was one of the first provinces that implemented PMTCT pilot studies. The PMTCT program was expanded in 2003 to all antenatal clinics and professional nurses were trained on PMTCT control, lay councillors were trained to provide HIV counselling and testing (HCT) and district officers provided additional support (17). In 2005 HCT was integrated with PMTCT services (17, 18). In 2007 the PMTCT program was evaluated in three sub-districts in the Free State as part of a wider study of PMTCT in four African countries.

Despite the presence of data showing the efficacy of a wide range of programs to prevent MTCT under ideal conditions in trials, there is a lack of understanding of the

health systems or operational requirements required for programs to be effective. Measuring HIV transmission rates is not sufficient as children born to HIV infected mothers but who do not become infected are at higher risk of morbidity and mortality compared to those that are not infected. Currently, there is no consensus gold standard to adequately measure population effectiveness of PMTCT programs and it is difficult to monitor the implementation of coordinated programs, where resources are constrained (19). In addition, there is a lack of complete and accurate routine information making it difficult to accurately measure effectiveness of programs (20, 21).

Problem statement

Although there have been significant advances in the implementation of PMTCT interventions particularly in sub-Saharan Africa, there were 390 000 new paediatric HIV infections in 2010 and over 90% occurred in sub-Saharan Africa (22). A developed, well-functioning and widely accessible health care system is a requirement for an effective PMTCT program. This is not the case in many resource limited settings as there are challenges including a lack of trained health care providers, poor client adherence, stock outs and a poor state of the physical infrastructure of the health care system (23).

Different approaches of measuring the effectiveness of PMTCT programs

Several techniques have been used to monitor the effectiveness of PMTC programs (15).This includes the use of mathematical modelling however accurate and reliable data is required for this purpose. A number of study designs have been used to monitor effectiveness (24-28).

Outcome measures

In this study HIV-free survival will be used to measure PMTCT effectiveness. It is an ideal measure particularly in resource poor settings like the Free State, because it not only measures the direct benefits of the program such as prevention of infections and deaths but it also integrates the benefits in children who are exposed but do not become infected with HIV. HIV-free survival measures both the quality of antenatal and obstetric care as well as post-natal care and evaluates PMTCT effectiveness at the population level rather than at the facility level only, as is usually the case in most studies.

Study rationale

Several studies have been conducted in lower and middle income countries to measure the effectiveness of PMTCT programs using different methodological approaches and outcomes. Most PMTCT studies have been limited to evaluating the effectiveness of interventions in preventing in utero and intrapartum transmission of HIV. These studies have provided little information on the long term effects of different feeding practices and ART prophylaxis provided to the mother and new-born, on the transmission of HIV and or child survival.

The outcome HIV-free survival is a better measure as it incorporates the effects in exposed children who do not become infected as well as factors associated with survival. Population-based studies such as household surveys have the added benefit of including women who may not have attended antenatal services or who did not deliver in a health care facility.

Objective

1. The primary objective will be to evaluate the effectiveness of the PMTCT program by comparing HIV-free survival in children less than two years of age, who have been exposed to HIV, with survival in unexposed children in Free State province. Factors associated with survival will also be determined.

.

2. The secondary objective of the study will be to determine risk factors that are associated with HIV transmission among children exposed to HIV, taking into account the PMTCT exposure status of the mother.

Methodology

Study design

This study will be a secondary analysis of data from the PEARL study that was a multi-country evaluation of the PMTCT program in communities in Cameroon, Côte d'Ivoire, South Africa, and Zambia between 2008 and 2009. This was a cross sectional community survey.

Study population

The study population was all women who had given birth to a child in the previous two years in the catchment area of maternity facilities in three randomly selected sub-districts in the Free Sate. Mothers were interviewed and socio-demographic information was collected. Blood was taken from mother and child for HIV-testing anonymously in the laboratory.

Sampling method

Study sampling was part of the original study. Multistage cluster sampling was employed. The catchment area for the maternity services in the three randomly selected areas, were mapped. The area was divided into clusters based on the census sub-areas and 30 out of 210 clusters were randomly selected. A random starting point was selected in each cluster. Systematic sampling was used and sampling was continued until the required number of households, with children born 2 years prior to the study were identified, and mothers consented to be included in the study.

Information about the survey was disseminated throughout the community by means of door to door sensitization, announcement of survey information, broadcasting on radio, involvement of local and familiar leaders that were known around the community, printed material to promote participation, questionnaire uptake and collection of blood specimens in the community

Mothers (who may be dead or alive) in the household were included in the study if they had given birth to a child. In cases where no one was home to participate in the interview, two additional attempts were made to identify an eligible mother in the household. The study was conducted between November 2007 and April 2008.

Sample Size

We hypothesize that survival will be lower in children born to HIV infected mothers. The required sample size was thus calculated by assuming 70% of children born to HIV-infected mothers would survive, whereas 90% of children born to uninfected mothers

would survive. As we wanted 80% power to detect this 20% difference with α=.05, we required a sample of 246 mother-infant pairs.

Data collection

Trained field workers interviewed mothers and collected the data under the supervision of trained supervisors and study coordinators. Field workers were women from the same communities where the study was being conducted. Interviewers were trained on the importance of ensuring privacy and confidentiality at all times. All identifiers were removed from the interview schedules once the interview was completed. The questionnaires were checked manually for errors during the fieldwork by supervisors and co-ordinators. Data was double captured by trained personnel.

Study questionnaire

The study questionnaire was based on several District Health Survey questionnaires used in different countries. Socio-demographic and socio-economic variables were collected at each household. These included type of water supply, level of education, and antenatal and delivery care received, with a special focus on PMTCT service utilization. The child questionnaire included the type of delivery, the medications given to the mother around birth and the weight of the infant at birth.

Table 1 shows variables that will be used to determine risk factors associated with HIV-free survival. These factors include demographic information including age, level of education, employment and education status of the mother. The variable received PMTCT was categorized into those who received any form of PMTCT and those who received no PMTCT. The study collected data on socio-demographics as well as socio-

economic status and data on water supply and electricity to assess general living conditions and the state of the environment.

Table .1. Variables that may be associated with HIV-free survival.

Variable	**Type**
Outcome (HIV status outcome of child)	Categorical-Binary
Negative	0
Positive	1
Sex of child	Categorical-Binary
Female	1
Male	0
Age of the mother	Categorical
<25	0
25-30	1
30-35	3
35-40	4
40+	5
Education level	Categorical-ordinal
No education	0
Primary	1
Secondary	2
Tertiary	3
Employment status	Categorical-Binary
Yes	1
No	0
Feeding status	Categorical
Exclusive breastfeeding	0
Replacement feeding	1
Mixed feeding	2
Mother received PMTCT prophylaxis	Categorical-Binary
Mother received any form of PMTCT prophylaxis	1
Mother received no PMTCT prophylaxis	0

Specimen collection and testing

All mothers with children born in the two years prior to the study, were asked to provide blood for HIV testing. Blood was obtained from children either by means of a heel-prick or finger-prick in order to obtain a dried blood spot. All blood tests were conducted anonymously in a laboratory after the field workers had left the household. Children of infected mothers were tested for HIV infection using HIV DNA PCR. Mothers were tested with rapid HIV antibody tests. The specimen collection was done only once written consent was obtained. All participants were advised to attend their local health clinic for individual HIV counselling and testing.

Reliability and Validity

The questionnaire was pretested before the study was commenced in order to identify the validity of the tool. A pilot study was conducted to determine the feasibility and acceptability of the study. A percentage of households were revisited to determine the reliability of data.

Data management and analysis plan

Data from the PEARL study will be obtained and captured using Microsoft Excel and the analysis will be performed on Stata 11 (StataCorp. 2012. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.). Descriptive and analytical statistics will be performed in order to understand the data using frequency tables, box and whisker plots and histograms. Furthermore, logistic regression analysis will be

performed to determine which of the risk factors are associated with HIV transmission and HIV-free survival.

Ethics

All data provided for this secondary analysis was anonymised before the initial four country analysis was conducted. There is no link to the name or address of participants. The protocol for this secondary analysis will be submitted to the Human Research Ethics committee of the University of Cape Town. The study will adhere to the principles as declared in the Helsinki Declaration of 2008 and the South African Medical Research Council guidelines on Ethics for Medical Research. There are no risks to participants as the data has already been collected. Potential benefits of the study include improved knowledge and understanding of the methodology to measure effectiveness of PMTCT programs over time. This will primarily benefit the health care system and the community of Free State province.

Dissemination of findings

The finding will be disseminated to stakeholders in the form of a report coupled with a brief presentation. The findings of the study will be disseminated to the broader scientific community by publishing the findings in a peer-reviewed journal.

References

1. Sherman GGL, R. R. Bhardwaj, S. Candy, S. Barron, P. Laboratory information system data demonstrate successful implementation of the prevention of mother-to-child transmission programme in South Africa. S Afr Med J. 2014;104(3 Suppl 1):235-8.

2. Organization WH. WHO Fact sheet N°360 2012. Available from: http://www.who.int/mediacentre/factsheets/fs360/en/.

3. UNAIDS. UNICEF update to a table published in the Joint United Nations Program on HIV/AIDS, Global Report: UNAIDS report on the global AIDS epidemic 2013,. 2013.

4. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. Lancet. 2012;379(9812):221-8.

5. Johnson K, Way A. Risk Factors for HIV Infection in a National Adult Population: Evidence From the 2003 Kenya Demographic and Health Survey. Journal of Acquired Immune Deficiency Syndromes. 2006;42(5):627-36.

6. Joy R, Druyts EF, Brandson EK, et al. Impact of neighborhood-level socioeconomic status on HIV disease progression in a universal health care setting. J Acquir Immune Defic Syndr. 2008;47(4):500-5.

7. Ruton H, Mugwaneza P, Shema N, et al. HIV-free survival among nine- to 24-month-old children born to HIV-positive mothers in the Rwandan national PMTCT programme: a community-based household survey. Journal of the International AIDS Society. 2012;15:18

8. Ahmad N. Molecular mechanisms of HIV-1 mother-to-child transmission and infection in neonatal target cells. Life sciences. 2011;88(21-22):980-6.

9. Cao Y, Krogstad P, Korber BT, et al. Maternal HIV-1 viral load and vertical transmission of infection: the Ariel Project for the prevention of HIV transmission from mother to infant. Nature medicine. 1997;3(5):549-52.

10. McGowan JP, Shah SS. Prevention of perinatal HIV transmission during pregnancy. Journal of Antimicrobial Chemotherapy. 2000;46(5):657-68.

11. Muula AS. HIV Infection and AIDS Among Young Women in South Africa. Croatian medical journal. 2008;49(3):423-35.

12. Boulle A, Van Cutsem G, Hilderbrand K, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. AIDS. 2010;24(4):563-72.

13. Forbes JC, Alimenti AM, Singer J, et al. A national review of vertical HIV transmission. AIDS. 2012;26(6):757-63.

14. Goga A DT, Jackson D, Dlamini N, Mosala T, Lombard T et al. Impact of the national prevention of mother-to-child transmission of HIV (PMTCT) program on perinatal mother-to-child transmission of HIV (MTCT) measured at six weeks postpartum, South Africa (SA). In: XIX International AIDS Conference. 2012:22–7

15. Stringer EM, Chi BH, Chintu N, et al. Monitoring effectiveness of programs to prevent mother-to-child HIV transmission in lower-income countries. Bull World Health Organ. 2008;86(1):57-62.

16. NDoH. The Sout African Antiretroviral Treatment Guidelines 2013.

17. Doherty T MB DS, Kamoga N, Stoops N, WaR LV. Case Study Reports on Implementation and Expansion of the PMTCT Programme in the Nine Provinces of South Africa. 2003.

18. Doherty T, Besser, M., Donohue, S., Kamoga, N., Stoops, N., Williamson, L. & Visser, R.2003a. "An evaluation of the prevention of mother-to-child transmission (PMTCT) of HI Vinitiative in South Africa: Lessons and Key Recommendations". 2003.

19. Stringer EM, Sinkala M, Stringer JSA, et al. Prevention of mother-to-child transmission of HIV in Africa: successes and challenges in scaling-up a nevirapine-based program in Lusaka, Zambia. AIDS. 2003;17(9):1377-82.

20. Doherty TM, McCoy D, Donohue S. Health system constraints to optimal coverage of the prevention of mother-to-child HIV transmission programme in South Africa: lessons from the implementation of the national pilot programme. Afr Health Sci. 2005;5(3):213-8.

21. Reithinger R, Megazzini K, Durako SJ, Harris DR, Vermund SH. Monitoring and evaluation of programmes to prevent mother to child transmission of HIV in Africa. British Medical Journal. 2007;334(7604):1143-6.

22. UNAIDS. UNICEF update to a table published in the Joint United Nations Program on HIV/AIDS, Global Report: UNAIDS report on the global AIDS epidemic 2013, 2013. Available from: http://www.unaids.org/en/resources/campaigns/globalreport2013/factsheet/.

23. Aizire J, Fowler MG, Coovadia HM. Operational issues and barriers to implementation of prevention of mother-to-child transmission of HIV (PMTCT) interventions in Sub-Saharan Africa. Curr HIV Res. 2013;11(2):144-59.

24. Goga AD, Thu-Ha; Jackson, Debra. Evaluation of the effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) programme measured at six weeks postpartum in South Africa, 2010. South African Medical Research Council, 2012.

25. Goga AE, Dinh T-H, Jackson DJ, et al. First population-level effectiveness evaluation of a national programme to prevent HIV transmission from mother to child, South Africa. Journal of Epidemiology and Community Health. 2014.

26. Goga AE DT, Jackson DJ for the SAPMTCTE study group. Evaluation of the Effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) Programme Measured at Six Weeks Postpartum in South Africa, 2010. South African Medical Research Council, 2010.

27. Kreiss J. Breastfeeding and vertical transmission of HIV-1. Acta Paediatr Suppl. 1997;421:113-7.

28. WoldesenbetS GA, Jackson DJ. The South African Programme to Prevent Mother to Child Transmission of HIV (PMTCT): Evaluation of Systems for Early Infant Diagnosis in Primary Health Care Facilities in South Africa: Report on Results of a Situational Assessment, 2010. 2012.

PART B

LITERATURE REVIEW

Introduction

Epidemiology of HIV/AIDS

HIV continues to be a major public health issue. By 2012, 36 million people had died as a result of HIV/AIDS and 1.6 million people died of AIDS related illnesses worldwide in 2012 alone (1). About 17.7 million women worldwide were living with HIV in 2012, and the prevalence of HIV among women between 30 to 34 years of age was the highest at 42.8 % in 2012 in South Africa alone (2). The majority of all infections (69%) are in sub-Saharan Africa (1). In addition, 9.7 million HIV-positive people were receiving ART in low and middle income countries in 2012. The Millennium Development Goal (MDG) number 6 calls for "prevention of infection among young people including information, HIV testing and condom provision, the prevention (eradication) of mother to child transmission, and improving treatment and care of children and young people infected with HIV". Hence the government attempted to meet the NSP's targets and reduce the MTCT rate of HIV to less than 5% by 2011 to meet the 4th and 6th Millennium Development Goals (MDGs) that were aimed at reducing by two thirds the under-five mortality rate between 1990 and 2015 (2).

Background

HIV/AIDS IN sub–Saharan Africa

Sub-Saharan Africa is the epicenter of the HIV pandemic with an estimated 25 million people living with HIV in this region. Furthermore, 2.9 million children younger than 15 years of age in sub-Saharan Africa are living with HIV and an estimated 190 000 deaths occurred in children in 2012 (3). There has been an increase in the prevalence of persons infected with HIV as the number of people receiving antiretroviral treatment has increased dramatically. A recent study in KwaZulu-Natal reported an increase in HIV prevalence among people aged between 15-49 years of age after scale-up of antiretroviral treatment in rural KwaZulu-Natal where the percentage of HIV infected people on ARVs increased from 0% in 2004 to 31% in 2011 and the prevalence of HIV increased from 21 to 29% (4). This increase in prevalence is a result of decreased mortality from AIDS as HIV positive people live longer. Approximately 49% of people living with HIV and in need of ART in the region were receiving therapy by the end of 2010 and 2 million people worldwide were newly enrolled on antiretroviral treatment in 2013 which was the largest ever annual increase (5). Three countries in sub-Saharan Africa with epidemics that are generalized, Botswana, Namibia and Rwanda have attained universal access to ART. In Swaziland and Zambia coverage is estimated to be 70% and 79% respectively (1). However the progress with coverage has been variable across sub-Saharan Africa.

In South Africa it is estimated that 6,300,000 people were living with HIV and 200,000 deaths occurred in 2013 (4). The highest prevalence being 19.1% amongst adults aged

between 15 to 49 years (4). In women older than 15 years of age 3,500,000 were living with HIV and there were 360,000 children less than 14 years of age living with HIV (4). A diagnosis of HIV infection is confirmed by blood tests which detect the presence HIV antibodies. Currently, there is no cure for HIV infection however it can be controlled through the effective use of antiretroviral therapy (ART).

Mother to child transmission of HIV (vertical transmission)

HIV can be transmitted from an HIV-infected woman to her child and this is called mother to child transmission of HIV (MTCT). It may occur during the course of the pregnancy, labour, delivery or during breastfeeding. In 2012 it was estimated that 1000 children were newly infected with HIV each day and the majority of these new infections were among children in sub-Saharan Africa (3). The coverage of prevention of mother to child transmission (PMTCT) services has substantially increased recently and fewer infants are acquiring HIV. In 2012 410 000 children aged between 0 to 14 years were living with HIV in South Africa. It is estimated that there had been a 49% decrease in the prevalence of HIV from 2002 to 2012 due to the introduction of PMTCT programs (6). The scaling up of antiretroviral programs had resulted in a 20% reduction in child mortality over the same period (7).

Several factors increase the risk of transmission of HIV from mother to child. HIV transmission from mother to child is high during delivery as the infant is exposed to blood and other fluids including amniotic fluid as they are passing through the birth canal, especially for those women who are not receiving any form of intervention. For HIV positive women who are not on treatment, there is 25% chance of passing the virus

to their child during pregnancy, labour, delivery and the risk of transmission is increased during breastfeeding by an additional 12% (8, 9). Feeding practice is one of the major factors that have been extensively investigated regarding transmission of HIV. Prior to the advent of the HIV epidemic, many studies showed that children who have been exclusive breast fed for the first six months of life were more likely to survive than children who received replacement feeding or mixed feeding. They were less likely to have diarrhoea, lower respiratory infections and otitis media. Initially children of HIV-infected mothers were advised to receive replacement feeding, as HIV transmission was more likely to occur through breast feeding. Recent studies show where mothers receive HAART and or infants receive ART prophylaxis, HIV transmission through breast feeding is unlikely and thus exclusive breast feeding is promoted in resource-limited settings, because of the risk of co-morbidities in children who are not breast fed. Even where mothers are not able to access HAART or ART prophylaxis for infants, the risk of death in in infants on replacement feeding exceeds the risk of MTCT through breastfeeding during the first 4 months of life, under conditions of poverty and poor hygiene and therefore exclusive breastfeeding is promoted. (10).

A cohort study was conducted in 2001 in Durban, South Africa including 551 pregnant women that were HIV positive who either exclusively breastfeed or formula feed. Those that were breastfeeding were encouraged to breastfeed for 3 to 6 months. The study found that infants who were exclusively breastfed for 3 months were less likely to acquire HIV in a period of 6 months compared to those who were never breastfed, the risk being 0.194 (95% CI 0.136-0.260) and 0.194 (95% CI 0.125-0.27) respectively (11). The effect of breastfeeding is more pronounced when the mother and infant are taking

ARVs during the period of breastfeeding (12-14). ARVs prevent replication of HIV and reduce the viral load in breastmilk (13). Re-infection with HIV during pregnancy is an important risk factor for transmission of HIV in utero, intrapartum and postpartum via breast milk. Risk doubles when compared with women with established infection because of high viral load associated with new infection (15, 16).

Socio economic status is associated with HIV status in women. Factors that affect socio-economic status include the "total measure of person's work experience and of individual's or family's economic and social positon in relation to others, based on income, education, and occupation" (17). A cross-sectional study in Kenya looking at the association between demographic, social, biological and behavioural variables and HIV serostatus found that wealth was positively associated with positive HIV serostatus. Women with primary education were more likely to be HIV infected than those with no education (OR=1.9) (18). Another study found unemployment was associated with delayed access to treatment for HIV (OR=1.41, 95% CI 1.14 to 1.74). Post-secondary education was associated with a reduced risk of becoming infected with HIV (HR=0.80, 95% CI: 0.71 to 0.91) (19). These finding were consistent with other studies (20, 21), but inconsistent with others (22, 23). Other studies show that the maternal age is associated with HIV. Children born to mothers aged between 15 to 24 years were more likely to be infected than children born to women of 35 to 39 years of age (24). Birth weight is also an important factor when investigating mortality due to HIV, low birth weight infants in particular have been reported to have a much higher risk of mortality and morbidity in infancy and early childhood (25, 26)

PMTCT interventions may reduce the rate of transmission to less than 1% (12, 14, 27). However, coverage is suboptimal as some pregnant HIV-infected women fail to access PMTCT services (28, 29). In 2012 the HIV prevalence among women attending antenatal services in the public sector in South Africa was 29.5% (95% CI: 28.8 - 30.2%). It has stabilized over the past 5 years. In 2011 vertical transmission of HIV was reported to be 2.7% (30). Despite the widespread implementation of PMTCT services in South Africa challenges still remain.

Exposure to HIV in utero, during delivery and through breast feeding has a substantial impact on morbidity and mortality, particularly in the first year of life. HIV-infected children demonstrate delays in development, deficits in functional health, increased opportunistic infections and highlight the need for increased uptake of early infant diagnosis and provision of ART for all infected infants (31-34). A cohort study in Malawi reported that HIV-infected children had significantly poorer health outcomes than HIV-unexposed children and HIV-exposed but uninfected children at 20 months. These included hospital admissions, delayed development, undernutrition and restriction in function (35). A meta-analysis in sub-Saharan Africa reported a cumulative mortality rate of 174/1000 live births among HIV-exposed children at 24 months (36). This further highlights the need for effective PMTCT programs to reduce child morbidity and mortality. The PMTCT Plus initiative where pregnant women are initiated on ART for life not only addresses vertical transmission of HIV but also impacts on the health and survival of the mother.

Review of evidence from PMTCT studies of ARV Prophylaxis

The earliest study of the efficacy of ARV prophylaxis to prevent MTCT was conducted in the United States of America (US). It was a randomized double blind controlled trial to determine the efficacy and safety of Zidovudine (ZDV) given during pregnancy and labour to the mother and to the infant for six weeks postpartum. HIV-positive women were randomly assigned to either short course Zidovudine (SC_ZDV) administered to mothers from 14 weeks of pregnancy and during delivery and for 6 weeks postnatal or placebo. The study showed a 66% reduction in the risk of transmission (37).The rate of transmission of HIV from mother to child was 22.6% in the placebo arm while it was 7.6% among those that were in the SC-ZDV arm. This trial was followed by various RCTs in Africa and Thailand.

The HIVNET012 trial conducted in Uganda provided nevirapine to mothers during labour and to infants within 72 hours of birth in the treatment arm and Zidovudine was given to mothers during labour and for 7 days thereafter to infants in the control arm in a breastfeeding population (37). Findings revealed a transmission rate of 11.8% in the treatment arm and 20.0% in the control arm at 6 to 8 weeks. This reduction was sustained at 18 months, with a rate of 15.7% and 25.8% in the treatment and control arms respectively (37). However, the biggest challenge was to rapidly translate study findings into policies to reach millions of HIV infected pregnant women in developing countries. The policy was difficult to implement in many African countries because of weak health care systems.

Strategies to prevent transmission of HIV

In developed countries with strong health systems the risk of vertical transmission of HIV has been reduced to less than 1%. A good PMTCT service requires a well-functioning health system (38). In order to decrease vertical transmission, antenatal care should include HIV counselling and testing and the receipt of prophylaxis for the HIV infected mother and infant. This requires well-functioning obstetric care antenatally and intrapartum and child health services postnatally. The minimum antiretroviral prophylactic regimen recommended in resource poor settings is single-dose nevirapine in labour because of its low cost, easy administration, rapid absorption and relatively long half-life. Best practice includes the provision of Highly Active Antiretroviral Treatment (HAART), delivery through elective caesarian section and appropriate feeding practices including either exclusive breast feeding if a mother has been on ARVS for 3 to 6 months and has an undetectable viral load or replacement feeding (39, 40). Replacement feeding is often not acceptable, feasible, safe or sustainable in resource limited settings (41, 42), and hence exclusive breastfeeding with antiretrovirals provided to the mother, is recommended (43, 44). In addition, with improved access to antiretrovirals (ARVs) more pregnant women are on ARVs before becoming pregnant. Current WHO guidelines recommend HAART for all HIV-positive pregnant women regardless of their CD4 count and they are encouraged to remain on treatment until they complete breastfeeding. A fixed-dose combination of three antiretrovirals is recommended to reduce the pill burden.

Challenges faced by PMTCT Programs in Sub-Saharan Africa

Antiretroviral programs encounter many challenges in sub-Saharan Africa(45). These challenges include the lack of trained personnel to initiate antiretroviral therapy and poorly developed drug procurement and distribution services. Health care workers require training on treatment, monitoring of adherence and counselling of HIV infected pregnant women. Viral load monitoring to effectively monitor the response to antiretroviral therapy is expensive and requires sophisticated technology that is not always available. These challenges are more complex in resource poor settings such as in South Africa (45-48).

PMTCT in South Africa

PMTCT rollout in South Africa

The first PMTCT program in South Africa was initiated by the Provincial Government of the Western Cape (PGWC) in Khayelitsha in 1999 despite being opposed from the National Ministry of Health at the time. The program included voluntary counselling and testing (VCT) and this was provided at one midwife obstetric unit (MOU) and AZT was dispensed by midwives from 36 weeks gestation and during labour. This was a pilot study that was later expanded to another MOU. However, there were no HIV services available for the mothers post delivery. Due to political resistance there was a delay in the implementation of PMTCT services elsewhere despite studies showing the effectiveness of PMTCT interventions. In 2002 the Western Cape launched the first province-wide PMTCT program despite resistance from the National Ministry of Health.

In 2003 pilot PMTCT programs were introduced in the rest of South Africa. Single-dose nevirapine (SD NVP) was offered to the mother in labour and to the infant within 72 hours of delivery. This intervention was coupled with modified obstetric practices, counselling on infant feeding options and free replacement feeding to HIV-positive mothers in order to avoid transmission through breastfeeding (49). Following the pilot programs, the South African government implemented the first nation-wide PMTCT program in 2004. In 2008 the national guidelines for pregnant women were amended by introducing dual therapy. Pregnant women received AZT from 28 weeks of pregnancy and Sd-NVP was provided during labour and to their infants with AZT. In addition provided-initiated counselling replaced voluntary counselling and testing.

The guidelines were further modified in 2010 to include routine HIV testing and counselling for all pregnant women. In addition women with a CD4+ T-cell count less than 350 cells/mm^3 were placed on HAART. In 2011 exclusive breastfeeding was recommended for all mothers and replacement feeding was reserved for medical conditions. In 2013, the guidelines were modified further to prioritise the initiation of HAART for women with severe HIV disease (WHO staging of either 3 or 4) regardless of their CD4 cell count. Currently HAART is recommended for all HIV-infected pregnant women with the use of a fixed dose combination of three ARV's to promote adherence.

PMTCT services in Free-State

In 2012 Free State had the third highest prevalence of HIV at 32.0% (95%CI 29.8 to 34.3%) among women attending ANC services in the public sector followed by KwaZulu-Natal and Mpumalanga (50). The first PMTCT pilot sites were initiated in 2001

in the Free State in 2 resource-limited sites in Frankfort and Virginia. Initially there was low rate of acceptance of HIV testing. In 2002 the sites ran out of rapid kits for testing for HIV for three months and during this period, specimens had to be sent to a central laboratory and hence there were missed opportunities for initiation of therapy as some of those women who tested failed to return to collect their results. The sites also ran out of nevirapine (51, 52). The Free State was the province with the highest rate of breast feeding in South Africa and 64% of mothers breastfed (51). In 2003 the PMTCT program was expanded to all antenatal services. Professional nurses were trained on the PMTCT protocol, operational plans were developed and implemented and replacement feeding was provided for those who chose that option. Lay counsellors were trained to provide HCT. In 2007 the PMTCT program was evaluated in three sub-districts in the Free State as part of a wider study of PMTCT in four African countries.

Despite the presence of data showing the efficacy of a wide range of programs to prevent MTCT under ideal conditions in trials, there is a lack of understanding of the health systems or operational requirements that are required for programs to be effective. Currently, there is no consensus gold standard to adequately measure population effectiveness of PMTCT programs and it is difficult to monitor the implementation of coordinated programs where resources are constrained (53). In addition, there is a lack of complete and accurate routine information making it difficult to accurately measure effectiveness of programs (54, 55). Studies are therefore required to evaluate and monitor effectiveness of PMTCT program and compare progress across programs.

Review of PMTCT effectiveness

Effectiveness is described as the prophylactic benefit in terms of intended and desired outcomes of a PMTCT intervention when applied in everyday practice (56). Effectiveness is a product of efficacy and coverage. If coverage is optimal, effectiveness should match the efficacy observed during clinical trials for the population in which the efficacy trial was conducted (56). Effectiveness is a function both of how much the prescribed therapy reduces the risk of mother to child transmission (MTCT) or efficacy and the proportion of the intended population at risk that accesses and uses the intervention correctly or coverage. Testing for HIV in antenatal clinics is the entry point into the PMTCT program and high coverage at every step helps reduce opportunities that may be missed to prevent MTCT and improve effectiveness. A study showed that coverage of HIV testing and receipt of results by mothers was 98.8% at antenatal services but there was a steady decline in coverage thereafter, but only 78.3% of those mothers that were HIV positive got a CD4 count, of whom 91.8% received appropriate ARV prophylaxis according to the protocol (57).

Several studies have been conducted to determine the efficacy of various ARV regimens administered during the intrauterine, intrapartum and postnatal period to reduce transmission of HIV from mother to child. When measuring effectiveness the numerator represents the number of people who are eligible for treatment who receive it, while the denominator represents the population at risk. Coverage is explained as the product of a pathway called the PMTCT cascade which consists of events that must occur in order for the prophylaxis to be administered (58, 59). The PMTCT cascade is built from indicators that are routinely collected by facilities that provide PMTCT. Figure

1. below details the steps of the cascade beginning with the woman agreeing to HIV testing, accepting the positive result, agreeing to be part of the program, accessing ART, adhering to the regimen, adhering to the infant regimen and HIV testing for the infant at 6 weeks and later if required. Each step of the cascade is critical in ensuring the success of the program as attrition at each point will have an impact overall. A study assessing the acceptability and effectiveness of a PMTCT program in Côte d'Ivoire and Burkina Faso showed that after testing positive for HIV, women refused short course ZDV during pregnancy and the overall coverage was low (58). Further studies in Cote d'Ivoire, Burkina Faso and Kenya showed that 60% of HIV-infected women refused the antiretroviral prophylaxis offered (58, 60). Reasons for rejecting prophylaxis included lack of education, not fully understanding the purpose of prophylaxis, denial and fear of stigma from members of the community (61)

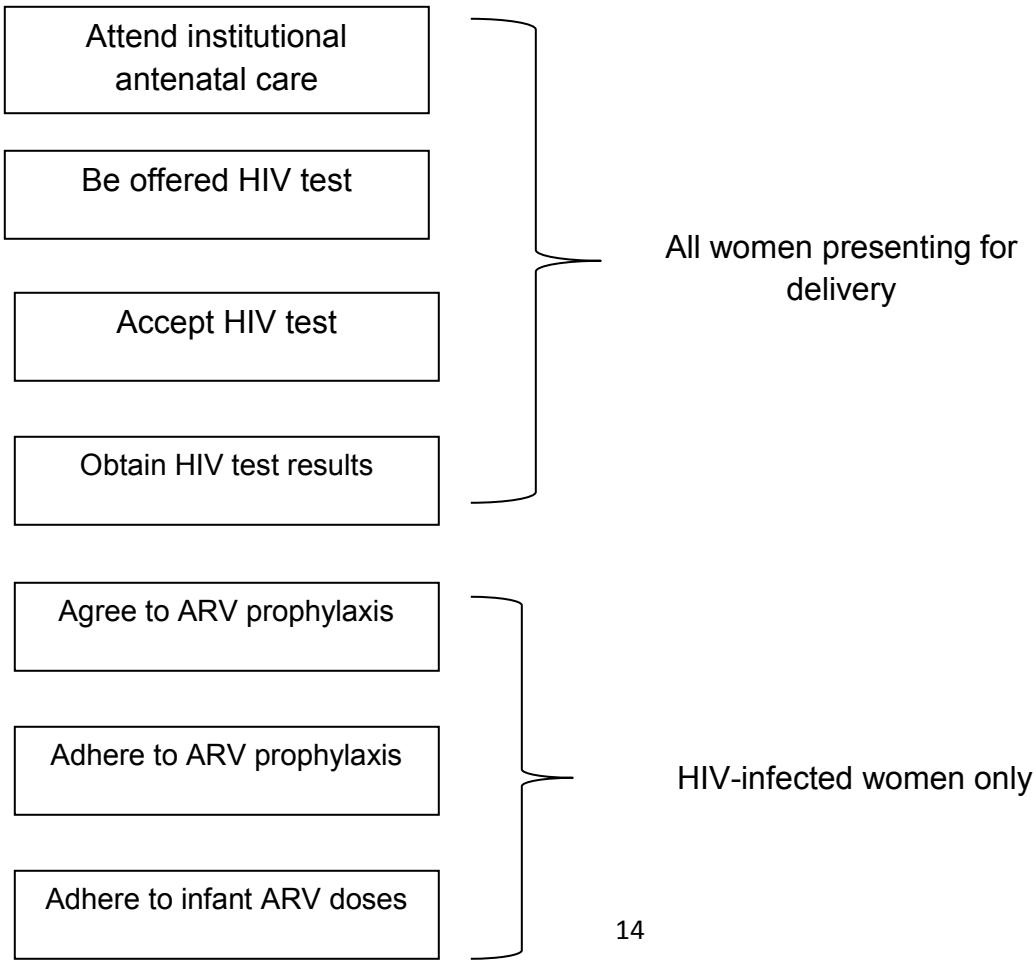

Figure 1. PMTCT cascade for coverage. Source (56)

Ways to evaluate PMTCT programs

PMTCT services are located in antenatal and maternity clinics and data are easily accessible for linking mother-infant pairs through medical records and data from the PMTCT cascade. It is also easy to acquire specimens, for example from cord blood after mothers have delivered. Data is collected at one point in time or retrospectively using facility-based studies (56, 62). Facility-based studies are convenient because sampling units can be easily obtained (62). These include facility based cross-sectional studies used to estimate program effectiveness that are simpler and less expensive than prospective designs as data are collected at one point in time or retrospectively. Measuring PMTCT effectiveness has been conducted through population-based surveys that gather cross-sectional or retrospective data. All households where a child (dead or alive) was born in the previous two years are identified and the HIV status of women who have delivered a child in the previous year and the HIV status of exposed children can be determined (54, 59, 63, 64). These studies are useful in describing the burden of disease and provide population based outcomes since the entire population is included in the study (56).

A cross sectional study was conducted in Khayelitsha in 2005 to measure PMTCT effectiveness. It used facility based approach to identifying infants born to HIV-infected mothers who accessed PMTCT. The study selected 535 mother-infant pairs from antenatal PMTCT registers and they were able to identify 71% of these mother-infant

pairs around six weeks of age. At that time mothers were given Zidovudine (AZT) from 34 weeks gestation and during labour, while those who received less than 2 weeks of AZT were also given single dose NVP in labour. The rate of transmission was 8.8% (95% confidence interval 6.2–10.9%). A limitation was that it could not be ascertained whether those that were untraced had died from HIV (62). The disadvantage of facility-based information is that it is limited to pregnant women who attend antenatal and delivery services, and there is no information on women who do not attend. Hence facility-based data may be biased towards better outcomes as women have attended services. Use of retrospective data in survey studies may detect trends over time. If the program has been running for a number of years, the survey can be used to compare outcomes that are stratified by the age of children and can provide cohort data that can evaluate the PMTCT program. A potential disadvantage of this survey approach is recall bias as it relies heavily on patient recall for information on PMTCT.

In 2005 the performance of South Africa's national pilot PMTCT program was reported using routine PMTCT program data collected from the 10 pilot sites from January to December of 2002. The study identified health system constraints to program effectiveness and optimal coverage. It showed that acceptance of HIV testing was poor, delivery of nevirapine to mothers was low and that it was difficult to track mothers postnatally to test infants at 12 months. Infant feeding practices suggested that there was inadequate counselling on the possible negative effects of replacement feeding (54). The study led to the review of feeding practices and recommendations on the importance of exclusive breast feeding.

The first major national evaluation to determine effectiveness of the PMTCT program was conducted in 2010. The study was a cross-sectional facility-based study which looked at MTCT rates 6 weeks postpartum at immunization sites in all 9 provinces. The study included 10 178 HIV exposed infants and the transmission was 3.5% (95 % CI 2.9 to 4.1). The uptake of services for PMTCT was high with 98% of women getting tested and 91.7% of those who were found to be positive received ARV prophylaxis. However only 35% of mothers indicated that they would take their infants for early infant diagnosis, indicating that opportunities to identify and care for HIV infected infants early would be missed (65). In 2011 a second facility based survey of PMTCT effectiveness was conducted. It was the first national evaluation of WHO Option A that included a change to exclusive breastfeeding in women who were taking ARVs. The study measured transmission rates in infants around 6 weeks of age attending immunization services. The survey found that vertical HIV transmission had decreased from 3.5% in 2010 to 2.7% (95% CI 2.1 to 3.2%) in 2011. In addition, the quality of counselling on infant feeding had improved and women were more likely to exclusively breast feed (66). Another study indicated that despite the fact that 95% of infants identified as exposed to HIV at antenatal clinics were tested for HIV, exposed infants of mothers who did not attend antenatal care and those who do not access HIV testing during antenatal and intrapartum care would be missed (67). A recent study using HIV PCR test data from 2003 to 2012 from the laboratory information system demonstrated that there had been rapid scale-up over the first decade of the PMTCT program, with 73% of the estimated 270 000 HIV-exposed infants having an early PCR test and that early

transmission had fallen to 2.4% as a result of successful implementation of the PMTCT program (68).

Other facility based studies have used the strategy of linking anonymous cord blood specimens to evaluate PMTCT effectiveness. Nevirapine is easily detected in cord blood through chromatography as it readily crosses the placenta, gets absorbed and has a long half- life. Coverage is determined from the proportion of mother-infant pairs of HIV infected women where there is evidence that both the mother and infant received antiretrovirals. As specimens are anonymous, consent is not required from women to test their cord blood (60, 69). In addition, data from clinical records can be linked to cord blood data. In 2008 cord blood from 3034 women was collected at delivery in the Western Cape. Of the 3034 specimens, 507 tested HIV positive, and 474 (92.7 %) were tested for the presence of ART. Fifty eight percent had evidence that the standard of care had been provided and 73% had ingested some form of ART prophylaxis. The cord blood surveillance indicated a much lower coverage than that reported in the clinical records (70).

In 2003 a similar study conducted in Zambia measured PMTCT effectiveness using cord blood specimens from 10194 women delivering in 10 public facilities. The coverage was only 30%. There was evidence of failures at a number of points in the PMTCT cascade with 18% of HIV positive mothers not being offered HCT and 27% declining testing, while 32% of women who were recorded as having been given nevirapine, there was no evidence of nevirapine in the cord blood. It was also found that women who refused testing during testing were more likely to be HIV positive. Another study evaluated effectiveness using cord blood in 2005 and of the 8787 women enrolled in the

study 2257 (26%) were HIV positive according to the cord blood. Of these women 1246 (55%) had received an antenatal HIV test result and only 1112 (89%) were positive according to the clinical records. Only 751 of 1112 (68%) positive women who were identified by the PMTCT program had evidence of NVP in the cord blood and only 675 infants (90%) received NVP before discharge. Adherence to both maternal and infant prophylaxis was only 30% (675/2257). The study showed that there were losses at each step of the cascade (59).

In 2004 a clinic based study conducted in KwaZulu-Natal evaluated effectiveness through anonymous HIV prevalence screening on dried blood spot (DBS) samples from all the infants who attended their 6 week immunization clinics. The study determined maternal infection by testing for HIV antibodies and for infection in exposed infants through PCR. Of the 931 infants who were exposed to HIV (37.4%; 95% confidence interval, 35.4–39.4%), 188 infants were HIV RNA positive, resulting in rate of transmission that was 20.2% (95% CI, 17.8–23.1%). The rate of transmission was 15.0% in mothers who had received single-dose nevirapine. This study was one of the first to demonstrate that HIV testing of all infants who attended immunization services at 6 weeks of age identified infected infants early, maximizing the opportunity for early treatment. The study showed that screening for HIV at immunization clinics was acceptable, feasible and beneficial (71).

Measuring effectiveness is also largely dependent on the type of data used for the study. Community-based data are more valuable because they provide a more representative sample as they include women who do not attend antenatal or delivery services. PMTCT effectiveness studies may be included in other population-based

studies such as Demographic Health Survey (DHS) studies. Some studies have used Demographic Health Surveys (DHS) which are simple and have been conducted in a number of countries to collect such population-based information. Programs that rely on women who accept testing during voluntary testing to determine HIV prevalence may under- or over-estimate the true prevalence (55).

Other studies have used the prospective follow up study design to measure effectiveness of PMTCT programs (60, 69, 72, 73). These studies observe participants and measure HIV-free survival and compare HIV transmission rates. Although measurement of HIV-free survival through cohort studies of large groups of mother-infant pairs is an ideal measure for measuring PMTCT effectiveness, the limitations include loss to follow up and high costs and hence cohort studies are not practical for routine monitoring. Individual behaviour may change when observed (the Hawthorne effect) and study findings cannot be generalized or applied to other populations (74). In addition, with most cohort studies, the investigators are ethically bound to provide standard of care and therefore should ensure that mothers are referred for appropriate care and this may affect the outcome (69).

In Côte d'Ivoire infants were followed for 12 months to evaluate the short term (4 week) and longer term (12 months) effectiveness of a two-tiered PMTCT strategy. Women meeting the WHO eligibility criteria received HAART and those with less advanced HIV disease were given short-course antiretroviral PMTCT prophylaxis. The study demonstrated that both short- and long-term PMTCT strategies were safe and effective in resource-constrained settings (75). Another study evaluated PMTCT program effectiveness in rural Kenya and in Cameroon where infants were followed for 24

months (60). In both studies loss to follow up was more than 20% introducing selection bias (60, 69). Another cohort study of antenatal clinic attendees was conducted in rural Kenya to determine the effectiveness of short-course ZVD for PMTCT in a breastfeeding population between 1996 and 1998. Of the 216 HIV-infected mothers followed for 24 months, 51 (23.6%) completed the regimen, 69 (31.9%) only competed the prepartum portion, and 96 (44.4%) never completed any portion of the regimen. The major reasons for nonadherence were the occurrence of labour earlier than expected and delivery at home. At 2 year, 75 of the children exposed to HIV (34.7%) and 33 HIV positive mothers (15.3%) had died and almost 30% of HIV exposed infants were lost to follow up. The HIV-free survival of children at 24 months of age was associated with survival of the mother and pre-partum ZDV compliance (60). These findings highlight the problems associated with the implementation of PMTCT programs in rural areas in Africa. There were also socioeconomic and cultural barriers to access to care. A further limitation of the study was selection bias as recruitment was voluntary and women with a life threatening illness and single women were excluded from the study. Another study conducted in Malawi determined the acceptability of voluntary counselling and testing for HIV. The study provided information on the prevention of HIV/AIDS, emphasizing mother to child transmission, after which mothers had the right to either delay or refuse test. The study included 3136 mothers attending antenatal services for the first time, and 2996 were counselled prior to testing, 2965 were tested for HIV, all of whom were post-test counselled. Thirty one mothers (1%) refused testing and 646 (22%) individuals were found to be HIV infected and 238 (45%) of these mothers and 222 (34%) of these infants received NVP. The cumulative loss to follow up was 358 (55%) by the 36-week

antenatal visit, 440 (68%) by delivery, 450 (70%) by the first postnatal visit and 524 (81%) by the 6 month postnatal visit. The majority of deliveries (87%) occurred at peripheral sites where PMTCT was not readily available (41).

Other studies of PMTCT effectiveness included observations of consultants and interviews with mothers attending clinics. One such study highlighted the need for training on counselling particularly regarding optimal infant feeding practices as this study showed poor quality of counselling and information provided (76).

In South Africa the prospective cohort study design was used to measure PMTCT effectiveness by following 665 mother/infant pairs where the mother was HIV positive. The study was conducted in three sites; Paarl (Western Cape), Rietvlei (Eastern Cape) and Umlazi (KwaZulu-Natal) between 2002 and 2004. The women and infants were followed for 36 weeks after birth with data collected during home visits until 9 months of age. Only 588 pairs (88.4%) were found 3 weeks postpartum. HIV transmission at 3 weeks of age was 8.6% (95% CI 4.5 to 14.5%) in Paarl, 13.7% (95% CI 8.9 to 19.8%) in Rietvlei and 11.9% (95% CI 8.3 to 16.3%) at Umlazi. A high HIV viral load was associated with the transmission of HIV or death (hazard ratio 1.54 95% CI, 1.21 to 1.95). The odds of transmission were 1.5 times higher in participants in the rural site compared to those in urban sites after adjusting for potential confounders such as socioeconomic status. This study found that PMTCT programs using Sd-NVP administered to both mother and child could reduce the early transmission of HIV. The study highlighted the need for a well-functioning integrated health system, for optimal implementation (72). This study also measured HIV transmission at 36 weeks. The cumulative transmission rate at 36 weeks of age was 15.3% in Paarl, 22.4% in Umlazi

and 25.6% in Rietvlei. Mortality differed across the 3 sites with Rietvlei showing substantially higher mortality. The study identified important predictors of effectiveness that needed to be addressed in order to optimize the effectiveness of PMTCT programs. These included emphasizing the importance of exclusive breastfeeding and eliminating the underlying and deep seated inequities South Africa health care system (73).

In 2002 a longitudinal study included 1234 HIV positive women who were given Sd-NVP and delivered at Coronation Women and Children's hospital. HIV transmission was 8.7% at 6 weeks and 8.9% at 3 months of age indicating the effectiveness of NVP along with replacement feeding in reducing the rate of transmission (77). Over 70% infants were lost to follow up by 4 months of age and this was the major limitation of this study.

Other studies have used the retrospective approach. Women attending ANC from 2004 to 2007 were included and 689 ARV naive women were started on HAART. The mean baseline HIV viral load was 101,561 copies/ml. Two percent of women who were initiated on stavudine, lamivudine, and nevirapine had an adverse drug reaction, viz. a skin rash associated with nevirapine. The CD4 cells/uL count increased by more than 50 in 80% and viral suppression to less than 1000 copies/ml was achieved in 81% of women. The rate of HIV transmission was 5% in the 302 mother-infant pairs who completed follow-up for post-natal care. Transmission was 0.3% in the women who received more than seven weeks of HAART during pregnancy showing that initiating pregnant women on HAART was highly effective (78).

Gap in knowledge

The HIV/AIDS burden globally continues to be a significant public health problem 30 years into the epidemic. Significant improvements to PMTCT services have been made over the years and have shown that vertical transmission can be reduced to less than 1% in women initiated on HAART. Several techniques have been used to monitor the effectiveness of PMTCT programs. Measuring transmission rates alone does not provide information on exposed children who do not become infected. It is therefore imperative to conduct studies that identify factors associated with HIV-free survival and transmission of HIV. These findings may be used to inform policy and improve the effectiveness of PMTCT programs.

References

1. WHO Fact sheet N°360 2012 2012. Available from: http://www.who.int/mediacentre/factsheets/fs360/en/.

2. (NDoH) NDoH. The South African Antiretroviral Treatment Guidelines 2010. 2010.

3. UNAIDS. UNICEF update to a table published in the Joint United Nations Program on HIV/AIDS, Global Report: UNAIDS report on the global AIDS epidemic 2013,. 2013.

4. Zaidi J, Grapsa E, Tanser F, Newell ML, Barnighausen T. Dramatic increase in HIV prevalence after scale-up of antiretroviral treatment. AIDS. 2013;27(14):2301-5.

5. Mofenson LM. Prevention in Neglected Subpopulations: Prevention of Mother-to-Child Transmission of HIV Infection. Clinical Infectious Diseases. 2010;50 (Supplement 3):S130-S48.

6. HSRC (2014). South African National HIV Prevalence, Incidence and Behaviour Survey 2012.

7. Coutsoudis A, Pillay K, Kuhn L, et al. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. AIDS. 2001;15(3):379-87.

8. Connor EM, Sperling RS, Gelber R, et al. Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. New England Journal of Medicine. 1994;331(18):1173-80.

9. Mofenson LM. Technical report: perinatal human immunodeficiency virus testing and prevention of transmission. Committee on Pediatric Aids. Pediatrics. 2000;106(6):E88.

10. De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. JAMA. 2000;283(9):1175-82.

11. Homsy J, Moore D, Barasa A, et al. Breastfeeding, mother-to-child HIV transmission, and mortality among infants born to HIV-Infected women on highly active antiretroviral therapy in rural Uganda. J Acquir Immune Defic Syndr. 2010;53(1):28-35.

12. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission: a randomised, double-blind, placebo-controlled trial. Lancet. 2012;379(9812):221-8.

13. Kreiss J. Breastfeeding and vertical transmission of HIV-1. Acta Paediatr Suppl. 1997;421:113-7.

14. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral Regimens in Pregnancy and Breast-Feeding in Botswana. New England Journal of Medicine. 2010;362(24):2282-94.

15. Eaton LA, Kalichman SC. Changes in Transmission Risk Behaviors Across Stages of HIV Disease among People Living with HIV/AIDS. The Journal of the Association of Nurses in AIDS Care. 2009;20(1):39-49.

16. Johnson K, Way A. Risk Factors for HIV Infection in a National Adult Population: Evidence From the 2003 Kenya Demographic and Health Survey. Journal of Acquired Immune Deficiency Syndromes. 2006;42(5):627-36.

17. Association AP. socioeconomic status. The American Heritage® New Dictionary of Cultural Literacy. 2005;3.

18. Joy R, Druyts EF, Brandson EK, et al. Impact of neighborhood-level socioeconomic status on HIV disease progression in a universal health care setting. J Acquir Immune Defic Syndr. 2008;47(4):500-5.

19. Lopman B, Lewis J, Nyamukapa C, et al. HIV incidence and poverty in Manicaland, Zimbabwe: is HIV becoming a disease of the poor? AIDS. 2007;21 Suppl 7:S57-66.

20. Barnighausen T, Hosegood V, Timaeus IM, Newell ML. The socioeconomic determinants of HIV incidence: evidence from a longitudinal, population-based study in rural South Africa. AIDS. 2007;21 Suppl 7:S29-38.

21. de Walque D, Nakiyingi-Miiro JS, Busingye J, Whitworth JA. Changing association between schooling levels and HIV-1 infection over 11 years in a rural population cohort in south-west Uganda. Tropical medicine & international health. 2005;10(10):993-1001.

22. Glynn JR, Carael M, Buve A, et al. Does increased general schooling protect against HIV infection? A study in four African cities. Tropical medicine & international health. 2004;9(1):4-14.

23. Ruton H, Mugwaneza P, Shema N, et al. HIV-free survival among nine- to 24-month-old children born to HIV-positive mothers in the Rwandan national PMTCT program: a community-based household survey. Journal of the International AIDS Society. 2012;15:4-.

24. Kourtis AP, de Vincenzi I, Jamieson DJ, Bulterys M. Antiretroviral drugs during breastfeeding for the prevention of postnatal transmission of HIV-1. Adv Exp Med Biol. 2012;743:173-83.

25. Markson LE, Turner BJ, Houchens R, et al. Association of maternal HIV infection with low birth weight. J Acquir Immune Defic Syndr Hum Retrovirol. 1996;13(3):227-34.

26. Mitgitti R, Seanchaisuriya P, Schelp FP, Marui E, Yanai H. Low birth weight infants born to HIV-seropositive mothers and HIV-seronegative mothers in Chiang Rai, Thailand. Southeast Asian J Trop Med Public Health. 2008;39(2):273-8.

27. Chopra M, Daviaud E, Pattinson R, Fonn S, Lawn JE. Saving the lives of South Africa's mothers, babies, and children: can the health system deliver? Lancet.374(9692):835-46.

28. Sprague C, Chersich MF, Black V. Health system weaknesses constrain access to PMTCT and maternal HIV services in South Africa: a qualitative enquiry. AIDS Res Ther. 2011;8:10.

29. Goga A DT, Jackson D, Dlamini N, Mosala T, Lombard T et al. Impact of the national prevention of mother-to-child transmission of HIV (PMTCT) program on perinatal mother-to-child transmission of HIV (MTCT) measured at six weeks postpartum, South Africa (SA). In: XIX International AIDS Conference. 2012:22–7

30. Paul ME, Shearer WT, Church JA. Reduction of maternal-infant transmission of human immunodeficiency virus type i with zidovudine treatment. Pediatrics. 1995;96(2):407.

31. Abubakar A, Van Baar A, Van de Vijver FJ, Holding P, Newton CR. Paediatric HIV and neurodevelopment in sub-Saharan Africa: a systematic review. Tropical medicine & international health. 2008;13(7):880-7.

32. Hesseling AC, Cotton MF, Jennings T, et al. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. Clinical infectious diseases. 2009;48(1):108-14.

33. Kimani-Murage EW, Norris SA, Pettifor JM, et al. Nutritional status and HIV in rural South African children. BMC pediatrics. 2011;11:23.

34. Madhi SA, Kuwanda L, Cutland C, Klugman KP. Five-year cohort study of hospitalization for respiratory syncytial virus associated lower respiratory tract infection in African children. Journal of clinical virology. 2006;36(3):215-21.

35. Landes M, van Lettow M, Chan AK, et al. Mortality and Health Outcomes of HIV-Exposed and Unexposed Children in a PMTCT Cohort in Malawi. PLoS ONE. 2012;7(10):e47337.

36. Newell ML, Coovadia H, Cortina-Borja M, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet. 2004;364(9441):1236-43.

37. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet. 1999;354(9181):795-802.

38. CDC. CDC. 2007.

39. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal hiv transmission: A randomized trial. JAMA. 2002;288(2):189-98.

40. Mofenson L. TAW, Rogers M., Campsmith M., Ruffo N.M., Clark J., Sansom S. . Achievements in public health. Reduction in perinatal transmission of HIV infection--United States, 1985-2005. Morb Mortal Wkly Rep. 2006;55(21):592-7.

41. Manzi M, Zachariah R, Teck R, et al. High acceptability of voluntary counselling and HIV-testing but unacceptable loss to follow up in a prevention of mother-to-child HIV transmission program in rural Malawi: scaling-up requires a different way of acting. Tropical medicine & international health. 2005;10(12):1242-50.

42. Nduati R, John G, Mbori-Ngacha D, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. JAMA. 2000;283(9):1167-74.

43. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. Lancet. 2003;362(9387):859-68.

44. Peter Barron a, Yogan Pillay b, Tanya Doherty c, et al. Eliminating mother-to-child HIV transmission in South Africa. Bull World Health Organ. 2012;91:70–4

45. Harries AD, Nyangulu DS, Hargreaves NJ, Kaluwa O, Salaniponi FM. Preventing antiretroviral anarchy in sub-Saharan Africa. Lancet 2001;358(9279):410-4.

46. De Baets AJ, Bulterys M, Abrams EJ, Kankassa C, Pazvakavambwa IE. Care and treatment of HIV-infected children in Africa: issues and challenges at the district hospital level. Pediatr Infect Dis J. 2007;26(2):163-73.

47. Fransman D, McCulloch M, Lavies D, Hussey G. Doctors' attitudes to the care of children with HIV in South Africa. AIDS Care. 2000;12(1):89-96.

48. Stevens W, Kaye S, Corrah T. Antiretroviral therapy in Africa. British Medical Journal. 2004;328(7434):280-2.

49. (NDoH) NdoH. Department of Health. Department of Health Annual Report April 2000 - March 2001.

50. (NDoH) NDoH. The Sout African Antiretroviral Treatment Guidelines 2013.

51. Doherty T, Besser, M., Donohue, S., Kamoga, N., Stoops, N., Williamson, L. & Visser, R.2003a. "An evaluation of the prevention of mother-to-child transmission (PMTCT) of HI Vinitiative in South Africa: Lessons and Key Recommendations". 2003.

52. Doherty T MB DS, Kamoga N, Stoops N, WaR LV. Case Study Reports on Implementation and Expansion of the PMTCT Programme in the Nine Provinces of South Africa. 2003.

53. Stringer EM, Sinkala M, Stringer JSA, et al. Prevention of mother-to-child transmission of HIV in Africa: successes and challenges in scaling-up a nevirapine-based program in Lusaka, Zambia. AIDS. 2003;17(9):1377-82.

54. Doherty TM, McCoy D, Donohue S. Health system constraints to optimal coverage of the prevention of mother-to-child HIV transmission programme in South Africa: lessons from the implementation of the national pilot programme. Afr Health Sci. 2005;5(3):213-8.

55. Reithinger R, Megazzini K, Durako SJ, Harris DR, Vermund SH. Monitoring and evaluation of programmes to prevent mother to child transmission of HIV in Africa. British Medical Journal. 2007;334(7604):1143-6.

56. Stringer EM, Chi BH, Chintu N, et al. Monitoring effectiveness of programs to prevent mother-to-child HIV transmission in lower-income countries. Bull World Health Organ. 2008;86(1):57-62.

57. Goga AD, Thu-Ha; Jackson, Debra. Evaluation of the effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) programme measured at six weeks postpartum in South Africa, 2010. South African Medical Research Council, 2012.

58. Meda N, Leroy V, Viho I, et al. Field acceptability and effectiveness of the routine utilization of zidovudine to reduce mother-to-child transmission of HIV-1 in West Africa. AIDS. 2002;16(17):2323-8.

59. Stringer JSA, Sinkala M, Maclean CC, et al. Effectiveness of a city-wide program to prevent mother-to-child HIV transmission in Lusaka, Zambia. AIDS. 2005;19(12):1309-15.

60. Songok EM, Fujiyama Y, Tukei PM, et al. The use of short-course zidovudine to prevent perinatal transmission of human immunodeficiency virus in rural Kenya. Am J Trop Med Hyg. 2003;69(1):8-13.

61. Painter TM, Diaby KL, Matia DM, et al. Women's reasons for not participating in follow up visits before starting short course antiretroviral prophylaxis for prevention of mother to child transmission of HIV: qualitative interview study. British Medical Journal. 2004;329(7465):543-.

62. Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS. 2004;18(6):887-95.

63. Sherman GGL, R. R. Bhardwaj, S. Candy, S. Barron, P. Laboratory information system data demonstrate successful implementation of the prevention of mother-to-child transmission programme in South Africa. S Afr Med J. 2014;104(3 Suppl 1):235-8.

64. Teeraratkul A, Simonds RJ, Asavapiriyanont S, et al. Evaluating programs to prevent mother-to-child HIV transmission in two large Bangkok hospitals, 1999-2001. J Acquir Immune Defic Syndr. 2005;38(2):208-12.

65. Goga AE DT, Jackson DJ for the SAPMTCTE study group. Evaluation of the Effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) Programme Measured at Six Weeks Postpartum in South Africa, 2010. South African Medical Research Council, 2010.

66. Goga AE DT, Jackson DJ for the SAPMTCTE study group. Early (4-8 weeks post-delivery) Population-level Effectiveness of WHO PMTCT Option A, South Africa. South African Medical Research Council, 2011.

67. WoldesenbetS GA, Jackson DJ. The South African Programme to Prevent Mother to Child Transmission of HIV (PMTCT): Evaluation of Systems for Early Infant Diagnosis in Primary Health Care Facilities in South Africa: Report on Results of a Situational Assessment, 2010. 2012.

68. Goga AE, Dinh T-H, Jackson DJ, et al. First population-level effectiveness evaluation of a national programme to prevent HIV transmission from mother to child, South Africa. Journal of Epidemiology and Community Health. 2014.

69. Ayouba A, Tene G, Cunin P, et al. Low rate of mother-to-child transmission of HIV-1 after nevirapine intervention in a pilot public health program in Yaounde, Cameroon. J Acquir Immune Defic Syndr. 2003;34(3):274-80.

70. Stinson K, Boulle A, Smith PJ, et al. Coverage of the prevention of mother-to-child transmission program in the Western Cape, South Africa using cord blood surveillance. J Acquir Immune Defic Syndr. 2012;60(2):199-204.

71. Rollins NC, Becquet R, Bland RM, et al. Infant feeding, HIV transmission and mortality at 18 months: the need for appropriate choices by mothers and prioritization within programmes. AIDS. 2008;22(17):2349-57.

72. Colvin M, Chopra M, Doherty T, et al. Operational effectiveness of single-dose nevirapine in preventing mother-to-child transmission of HIV. Bulletin of the World Health Organization. 2007;85:466-73.

73. Jackson DJ, Chopra M, Doherty TM, et al. Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV-1. AIDS. 2007;21(4):509-16.

74. Gillespie SM CY, Lemp G, Arthur R, Buchbinder S,, (1991) ea. Progressive multifocal leukoencephalopathyin persons infected with human immunodeciency virus, San Francisco,1981–1989. Ann Neurol. 1991;30:597–604.

75. Tonwe-Gold B, Ekouevi DK, Viho I, et al. Antiretroviral Treatment and Prevention of Peripartum and Postnatal HIV Transmission in West Africa: Evaluation of a Two-Tiered Approach. PLoS Med. 2007;4(8):e257.

76. Chopra M, Doherty T, Jackson D, Ashworth A. Preventing HIV transmission to children: quality of counselling of mothers in South Africa. Acta Paediatr. 2005;94(3):357-63.

77. Sherman GG, Jones SA, Coovadia AH, Urban MF, Bolton KD. PMTCT from research to reality - results from a routine service : original article2004; 94(4):[p.289-92 pp.]. Available from: http://reference.sabinet.co.za/webx/access/electronic_journals/m_samj/m_samj_v94_n4_a18.pdf.

78. Black V, Hoffman RM, Sugar CA, et al. Safety and Efficacy of Initiating Highly Active Antiretroviral Therapy in an Integrated Antenatal and HIV Clinic in Johannesburg, South Africa. Journal of acquired immune deficiency syndromes (1999). 2008;49(3):276-81.

PART C

JOURNAL MANUSCRIPT

The Paediatric Infectious Diseases

Journal

Measuring PMTCT effectiveness through HIV free survival in children under 2 years

Tembeka Sineke,BSc *[1]

Corresponding author: Tembeka Sineke. School of Public Health and Family Medicine , University of Cape Town, Anzio Road, Cape Town 7925 South Africa. tsineke@gmail.com

Key words: Free State, South Africa, PMTCT, transmission, survival, multivariate analysis

Abbreviated title: PMTCT Effect. and HFS

Pediatr Infect Dis J

Running Title: PMTCT effectiveness in Free State.

Abstract

Background: Prevalence of HIV in pregnant women is 30% in the Free State province in South Africa and PMTCT services are widely available. The aim was to determine effectiveness of PMTCT program by measuring HIV transmission and HIV-free survival in children less than two years of age.

Methods: This was a secondary analysis of data collected from a cross sectional community household survey, using multistage cluster sampling. Women who had given birth two years prior to the study in the catchment area of three sub-districts that were randomly selected in Free State were included. Field workers interviewed mothers, identified children who had died. Logistic regression was used to determine risk factors.

Results: HIV exposure and outcome status was known for 874 (75.50%) of 1158 children under 2 years of age identified. Ninety seven children (11.10%) were exposed to HIV. One exposed (1.03%) and HIV positive child died from an HIV related illness while another exposed but uninfected child (1.03%) died from other causes. Thirty unexposed children died (3.86%). There was 72% reduction in survival in children who were hospitalised at least once since birth while those who breastfed at the time of interview were 5.08 times more likely to survive ($p<0.001$). Being hospitalized at least once since birth ($p<0.001$) was associated with transmission in the adjusted analysis.

Conclusion: Breast feeding and being admitted to hospital at least once since birth were significantly associated with survival and further research is recommended on the impact of these factors on transmission and survival.

Key words:Free State, South Africa, PMTCT, transmission, survival, multivariate analysis

Abbreviations:

HIV: Human immunodeficiency virus

AIDS: acquired immune deficiency syndrome

PMTCT: Prevention of mother to child transmission

Introduction

The burden of HIV/AIDS continues to be a significant public health problem globally 30 years into the epidemic (1). There have been 36 million deaths since the start of the epidemic and there were 35.3 million people living with HIV and 1.6 million people died due to AIDS worldwide in 2012 (2, 3). Sub-Saharan Africa is home to the majority of those infected despite the decline in new infections over the past 10 years (2). South Africa in particular has one of the largest epidemics with a prevalence of 15.9% among adults and 16.4% among women aged between 15 and 49 years (4). Free State province has the third highest prevalence of HIV with 32.0% of women attending antenatal services in the public sector being HIV infected in 2013 (5).

HIV can be transmitted from an HIV-infected woman to her child. The risk of vertical transmission can be reduced to less than 1% depending on the prophylactic regimens used for the mother and infant (6).

Several study designs have been used to monitor the effectiveness of PMTCT programs (7). There is a lack of a standard and clear model to evaluate effectiveness of PMTCT programs. Measuring transmission rates alone is not sufficient as children born to HIV infected mothers but who do not become infected are at higher risk of morbidity and mortality compared to those born to uninfected mothers.. Measuring HIV-free survival could be a useful tool to measure effectiveness. The aim of the study was to determine the effectiveness of the PMTCT programs by measuring the rate of

transmission and HIV-free survival among children younger than 2 years of age in the Free State.

Methodology

Study design

This study was a secondary analysis of the Free State data from a cross sectional survey that was conducted in 6 communities in four countries (South Africa, Cameroon, Zambia and Côte d'Ivoire) between November 2008 and April 2009. The South African study included Botshabelo, Thabo Mofutsanyana and Mantsopa sub-districts in Free State Province. This was a cross sectional community survey.

The study population was all women who had given birth to a child in the previous two years in the catchment area of maternity facilities in three randomly selected sub districts in the Free Sate. Mothers were interviewed and socio-demographic information was collected. Blood was taken from mother and child for HIV-testing anonymously in the laboratory.

Sampling method

Study sampling was part of the original study. Multistage cluster sampling was employed. The catchment area for the maternity services in the three areas randomly selected in the Free State, were mapped. Clusters were defined from the census sub-areas and 30 out of 210 clusters were randomly selected. A random starting point was selected in each cluster. Systematic sampling was used and sampling was continued

until the required number of households with children born in the previous two years was identified, and mothers consented to be included in the study.

Sample size

We hypothesized that children exposed to PMTCT will have a higher HIV-free survival rate compared to those who are not. The required sample size was calculated by assuming 70% of children born to HIV-infected mothers would survive whereas 90% of children born to uninfected mothers would survive. As we wanted 80% power to detect this 20% difference with α=.05, we required a sample of 246 mother-infant pairs.

Mothers (who may be dead or alive) in the household were included in the study if they had given birth to a child in the two years prior to the study. The study was conducted between November 2007 and April 2008. In cases where no one was home to participate in the interview, two additional attempts were made to identify an eligible mother in the household.

Data collection

Trained field workers interviewed mothers and collected the data under the supervision of trained supervisors and study coordinators. Field workers were women from the same communities where the study was being conducted. Interviewers were trained on the importance of ensuring privacy and confidentiality at all times. All identifiers were removed from the interview schedules once the interview was completed. The questionnaires were checked manually for errors during the fieldwork by supervisors and co-ordinators. Data was double captured by trained personnel.

Instrument

Study questionnaire

The study questionnaire was based on several District Health Survey questionnaires used in different countries. Socio-demographic and socio-economic variables were collected at each household. These included type of water supply, level of education, and antenatal and delivery care received including PMTCT service utilization. The child questionnaire included the type of delivery, the medications given to the mother around birth and weight of the infant at birth.

Measurement

Outcome measures

The main outcomes were HIV-free survival and the exposures were factors associated with HIV transmission. All mothers of children under two years of age were asked to provide blood for HIV testing. The specimen collection was done only once written consent was obtained. All participants were advised to attend their local health clinic for individual HIV counselling and testing. Consenting mothers were tested using rapid HIV antibody tests and the children of seropositive mothers were tested using HIV DNA PCR tests at an external site once all identifiers had been delinked.

Reliability and validity

The questionnaire was pretested before the study was commenced in order to identify the validity of the tool. A pilot study was conducted to determine the feasibility and

acceptability of the study. A percentage of households were revisited to determine the reliability of data.

Ethical review

All data provided for this secondary analysis was anonymised and there was no link to the name or address of participants. This study was approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (reference number: HREC REF: 271/2014) (**Appendix 1**).

Informed consent was obtained before a mother was accepted for the study and before blood was collected from a mother or child. Blood was tested in a laboratory once the collection of all data was complete and the name of all subjects was removed from the record. All test results were thus anonymous. In addition, the risk to subjects was minimal. Phlebotomy was conducted by a registered nurse. The rights of the patients were not violated and access to health care was not affected.

Data management and analysis

Data from questionnaires was coded and entered on to MS Access data which was exported onto STATA, version 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.) software. Statistical tests including the chi-squared test and Fisher's exact test, were performed on categorical variables that were chosen based on clinical knowledge. Data were explored using univariate analysis to compute distributions and summary statistics. A bivariate analysis determined associations with the outcome HIV free survival. Logistic regression was used to predict

variables associated with HIV free survival. The log likelihood ratio and Akaike information criterion (AIC) were used to select the best fitting model. A p-value of <0,05 identified statistical significance. The analysis included exposure variables such as age of mother, level of education attained, employment status, feeding practices, and whether they had received some form of PMTCT prophylaxis and the outcome variable was survival as well as HIV transmission. PMTCT coverage was defined as any form of PMTCT received, including SD NVP. Survival was compared in children exposed to HIV, where the mother received PMTCT and where the mother received no form of PMTCT and in children unexposed to HIV. The study also modelled factors associated with HIV transmission among children exposed to HIV.

Results

In the three areas where the study was conducted a total of 1158 children had been born in the previous two years and these mother-child pairs were eligible for the current study (Figure 1**)**. Of the 1158 children under 2 years, 284 (24.5%) had missing information on the HIV status of the mother. This was either because the mothers refused to participate, agreed to participate and were interviewed but refused to provide HIV specimens or because the data were missing.

The final analysis included 874 (75.50%) children. A total of 97 (11.10%) were exposed to HIV. Of the exposed, 21 (21.65%) were HIV positive and 76 (78.35%) were HIV negative and 19 (20%) were not exposed to PMTCT, 76 (80%) were exposed to PMTCT and 2 had missing PMTCT status. One of the HIV positive children died from an

HIV related illness. One other exposed but uninfected child died from other causes. Thirty unexposed children (3.86%) died.

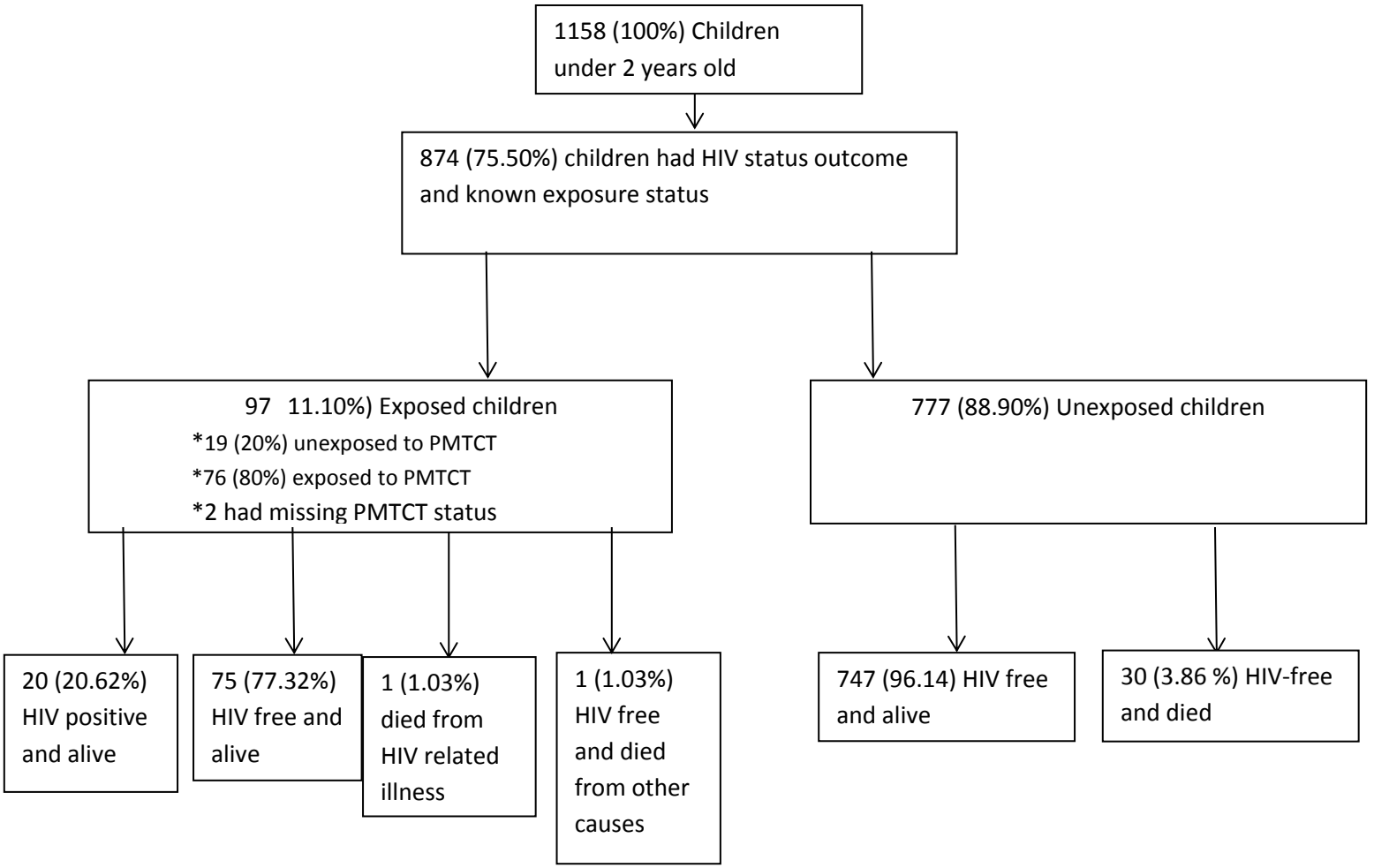

Figure 1. HIV status of mothers and children under 2 years eligible for the study in Free State

Table 1 shows the characteristics of mother-child pairs. There were more male than female children under two years of age (53.20% and 46.80% respectively). The median age of the mother was 24 years (range 15 to 52 years) and 11.10% of children were exposed to HIV and 79.38% of HIV-infected mothers were exposed to some form of PMTCT. There were more mothers aged between 15 and 24 years compared to 25 to 34 years and more women had a normal vaginal delivery than a caesarian section (85.98% compared to 14.08%). Table 1.1 shows the characteristics of exposed children included in the study. Nine children born to HIV positive mothers who were taking some form of antiretroviral prophylaxis (11.84%) became infected while 10 children born to mothers who were not taking any form of antiretroviral prophylaxis (52.63%) became infected. The majority of households had electricity and piped water (93.13% and 92.45% respectively).

Difference in survival between 2 groups of children

Table 2.1 presents survival in exposed children stratified by exposure of the mother to any form of PMTCT prophylaxis. Among the children born to HIV positive mothers who were taking some form of antiretroviral prophylaxis, 74 (97.37%) of the 76 survived. Among the children who were born to HIV positive mothers who were not taking any form of antiretroviral prophylaxis 19 (100%) survived. There was no significant difference (p=0.638) in survival comparing HIV exposed children whose mothers received some form of PMTCT prophylaxis compared to those who did not. Table 2.2 shows that mothers who did not receive any form of PMTCT were 8.27 times more likely to transmit HIV to their child.

Factors associated with survival

There were no significant differences in the characteristics of the mothers of children that survived and that did not survive (Table 3).

Table 4 presents the characteristics of children stratified by survival**.** There were no significant differences when comparing those children who were alive and those who had died.

Modelling variables associated with transmission

Table 5 presents the characteristics of the mother and child associated with HIV transmission in exposed children providing both crude and adjusted measures. The crude model showed that mothers of HIV infected children were significantly more likely to be under 25 years of age, and have not received any form of PMTCT prophylaxis. Children who had not received any form of PMTCT prophylaxis, who had been hospitalised at least once since birth, and who lived in households without tapped water were more likely to be infected. No variables were significantly associated with transmission in the adjusted multivariate analysis besides a child being hospitalized at least once since birth.

1.1. Modelling variables associated with survival

Table 6 shows the variables associated with survival in children providing both adjusted and unadjusted odds ratios. In the multivariate analysis only two variables were significantly associated with survival. There was a 72% reduction in survival in children who had been hospitalised at least once since birth while those who were still breastfed at the time of interview were 5.08 times more likely to survive.

Discussion

This study showed that PMTCT was not associated with a reduction in HIV transmission in HIV-exposed children less than two years of age in the multivariate analysis and that the strongest predictor of survival in both exposed and unexposed children was exclusive breast feeding and having been admitted to hospital at least once since birth (8).

Exclusive breast feeding is best practice for all children for the first six months of life and prior to the advent of HIV had been shown to decrease morbidity and mortality. One study reported that morbidity due to diarrhoea and lower respiratory tract and ear infections was twice as likely in children who were never breastfed (9). Although HIV is transmitted in breast milk, studies show a 3 to 4 fold reduction in transmission where children were exclusive breastfed for the first six months compared to children who were mixed fed. HIV exposed children who were exclusively breastfed until 6 months of age had lower mortality than children who received replacement or mixed feeding in a study in Zimbabwe (10). Studies show that this reduction was greatest where the

mother and/or child were receiving ARV prophylaxis (10-12). Replacement feeding is often not feasible and may be unacceptable particularly in resource limited settings, hence exclusive breastfeeding is recommended. This study showed that being breastfed at the time of the interview was significantly associated with survival.

Hospitalization of children at least once since birth was associated with decreased survival. However it could not be ascertained whether the hospitalization was due to HIV infection. These finding are similar to other studies that have reported multiple admissions to hospital in young children who die before the age of 2 years (13). This may be explained by the increased risk of opportunistic infections in HIV infected children (14, 15).

This study did not identify any factors associated with HIV transmission from mother to child. This is contrary to other studies that reported that education level attained, maternal age and mode of delivery were associated with HIV transmission and survival (16-19).

Studies have shown that children exposed to HIV have poorer outcomes than children who have not been exposed. Survival rather than HIV transmission is thus a more appropriate way of monitoring the effectiveness of PMTCT programs. However in this study, there was no difference in survival in unexposed children, compared to exposed children irrespective of whether the mothers received some form of PMTCT or not. The study was conducted in 2008 when the guidelines for PMTCT only included the use of SD NVP which was given to the mother at the commencement of labour and to the child within 72 hours of delivery. There have been major changes in PMTCT guidelines and

current guidelines in South Africa include HAART for all pregnant women. Yet even with a simple intervention using SD NVP, only 80% of women received it during labour and 74% of children received prophylaxis post-natally. This is likely to be due to losses at each step of the PMTCT cascade. The overall transmission rate of HIV in women who did not receive any form of PMTCT prophylaxis was surprisingly high (53%). Studies show that in the absence of any form of intervention there is a 25–45% risk of HIV transmission during pregnancy, delivery or breastfeeding (20-23). Transmission from mothers who received PMTCT was 12%. The HIVNET 012 RCT in Uganda (24) using SD NVP showed that transmission can be reduced by 47% and these results were corroborated by the South African Intrapartum Nevirapine Trial (SAINT) study which showed that giving a dose of NVP to both mother and infant during labour and after delivery was as effective as the HIVNET study in reducing the rate of perinatal transmission. Other studies have demonstrated that MTCT can be reduced to less than 1% in well-functioning programs (25) and best practice includes the provision of HAART, delivery through elective caesarian section and either exclusive breast feeding if a mother has been on ARVS for 3 to 6 months and has an undetectable viral load or replacement feeding (6, 25-28) where feasible. SD NVP is the simplest PMTCT strategy and although it is not the most effective, it should be the minimum intervention in resource-constrained settings (29, 30) or where health systems are weak (31).

Although not significant in the adjusted analysis, vertical HIV transmission was less likely to occur from mothers who were 25 to 35 years of age compared to those between 15 and 24 years of age. This could be due to the fact that mothers in the younger age group were recently infected with HIV and had high HIV viral loads (32-35).

Studies show that increased maternal viral load is associated with increased risk of HIV transmission (33).

Studies have shown that socio-economic status is associated with vertical transmission. In this study electricity and tapped water in the home were used as proxy indicators for socio-economic status. Socio-economic status is a generic term that attempts to describe the underlying economic position of individuals but it is difficult to measure accurately in research because it encompasses many parameters. In this study these proxy indicators were not significantly associated with vertical transmission in the multivariate analysis. A study in Kenya showed that a delay in initiating PMTCT treatment was 1.41 times more likely for people who were unemployed and had low socio-economic status (36). Socio-economic status may not directly affect MTCT but could contribute to factors that result either in decreased access to treatment or less effective treatment.

Although elective caesarian section (before the onset of labour or rupture of membranes) has been shown to reduce the risk of transmission of HIV by approximately 50% (24) caesarian section was not protective in this study. In this setting routine elective caesarian section is not feasible for all HIV infected women and thus it is not surprising that a protective effect was not seen as caesarian section was only performed for obstetric reasons (37, 38).

Study limitations

This study had a number of limitations. The study may not have been sufficiently powered to detect factors associated with transmission and survival. During the multivariate analysis variables were removed due to collinearity and this also affected the sample size.

Approximately 25% of mother-child pairs had missing data on HIV status. It is possible that mothers who refused HIV testing were more likely to be HIV infected as shown in household surveys in Zambia (39). This is corroborated by the fact that the prevalence of HIV in women in this study was lower than expected. In addition the study relied on participant recall and information bias such as social desirability bias may have been introduced. Information about the mother and the child was provided by the guardian in cases where the mother had died. This may have led to further bias.

The calculation of rates using person time would have been a more appropriate way of determining survival for this study. However, the date of death was not available or could not be verified for most of the children who died and this was a further limitation.

Almost 25% of mothers refused to consent to participate in the study and their HIV status was not known. There could have been systematic differences between mothers who consented to be part of the study and those who did not. It was not possible to identify non-responders and determine if they were different to responders. Although data was available on breast feeding it was not clear which children had been exclusively breast fed until 6 months of age.

Conclusion

This study showed breast feeding and being admitted to hospital at least once since birth were significantly associated with survival irrespectively of HIV exposure. PMTCT remains one of the most cost effective ways of combating the HIV/AIDS epidemic and reducing child mortality. ARV treatment is most effective when accompanied by other preventive methods including appropriate child feeding options and delivery by caesarean section. Further research should be conducted to measure the effectiveness of PMTCT programs by determining HIV free survival among children less than 2 years of age since the introduction of the new guidelines in 2010.

References

1. Ortblad KF, Lozano R, Murray CJ. The burden of HIV: insights from the Global Burden of Disease Study 2010. AIDS. 2013;27(13):2003-17.

2. UNAIDS. UNICEF update to a table published in the Joint United Nations Program on HIV/AIDS, Global Report: UNAIDS report on the global AIDS epidemic 2013. Available from: http://www.unaids.org/en/resources/campaigns/globalreport2013/factsheet/

3. World Health Organization. WHO Fact sheet N°360 2012 2012. Available from: http://www.who.int/mediacentre/factsheets/fs360/en/

4. Africa SS. Mid-year population estimates 2013.

5. NDoH. The South African Antiretroviral Treatment Guidelines 2013. 2013.

6. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. Lancet. 2012;379(9812):221-8.

7. Stringer EM, Chi BH, Chintu N, et al. Monitoring effectiveness of programmes to prevent mother-to-child HIV transmission in lower-income countries. Bull World Health Organ. 2008;86(1):57-62.

8. Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS. 2004;18(6):887-95.

9. Coutsoudis A, Pillay K, Kuhn L, et al. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. AIDS. 2001;15(3):379-87.

10. Iliff PJ, Piwoz EG, Tavengwa NV, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. AIDS. 2005;19(7):699-708.

11. Coovadia HM, Rollins NC, Bland RM, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. Lancet.369(9567):1107-16.

12. Kuhn L, Sinkala M, Kankasa C, et al. High Uptake of Exclusive Breastfeeding and Reduced Early Post-Natal HIV Transmission. PLoS ONE. 2007;2(12):e1363.

13. Gupta A, Nayak U, Ram M, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005. Clinical infectious diseases. 2007;45(2):241-245

14. Hesseling AC, Cotton MF, Jennings T, et al. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. Clinical infectious diseases. 2009;48(1):108-14.

15. Madhi SA, Kuwanda L, Cutland C, Klugman KP. Five-year cohort study of hospitalization for respiratory syncytial virus associated lower respiratory tract infection in African children. Journal of clinical virology. 2006;36(3):215-21.

16. Albrecht S, Semrau K, Kasonde P, et al. Predictors of Nonadherence to Single-Dose Nevirapine Therapy for the Prevention of Mother-to-Child HIV Transmission. Journal of acquired immune deficiency syndromes. 2006;41(1):114-8.

17. Bii SC, Otieno-Nyunya B, Siika A, Rotich JK. Self-reported adherence to single dose nevirapine in the prevention of mother to child transmission of HIV at Kitale District Hospital. East Afr Med J. 2007;84(12):571-575.

18. Kiarie JN, Kreiss JK, Richardson BA, John-Stewart GC. Compliance with antiretroviral regimens to prevent perinatal HIV-1 transmission in Kenya. AIDS. 2003;17(1):65-71.

19. Peltzer K, Mlambo M, Phaswana-Mafuya N, Ladzani R. Determinants of adherence to a single-dose nevirapine regimen for the prevention of mother-to-child HIV transmission in Gert Sibande district in South Africa. Acta Paediatr. 2010;99(5):699-704.

20. Nkwo PO. Prevention of Mother to Child Transmission of Human Immunodeficiency Virus: The Nigerian Perspective. Annals of Medical and Health Sciences Research. 2012;2(1):56-65.

21. Kourtis AP, Lee FK, Abrams EJ, Jamieson DJ, Bulterys M. Mother-to-child transmission of HIV-1: timing and implications for prevention. Lancet Infect Dis. 2006;6(11):726-32.

22. Lauer JA, Betran AP, Barros AJ, de Onis M. Deaths and years of life lost due to suboptimal breast-feeding among children in the developing world: a global ecological risk assessment. Public Health Nutr. 2006;9(6):673-85.

23. Watts DH. Management of Human Immunodeficiency Virus Infection in Pregnancy. New England Journal of Medicine. 2002;346(24):1879-91.

24. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of

HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet. 1999;354(9181):795-802.

25. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal hiv transmission: A randomized trial. Jama. 2002;288(2):189-98.

26. Kourtis AP, de Vincenzi I, Jamieson DJ, Bulterys M. Antiretroviral drugs during breastfeeding for the prevention of postnatal transmission of HIV-1. Adv Exp Med Biol. 2012;743:173-83.

27. Mofenson LM. Technical report: perinatal human immunodeficiency virus testing and prevention of transmission. Committee on Pediatric Aids. Pediatrics. 2000;106(6):E88.

28. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral Regimens in Pregnancy and Breast-Feeding in Botswana. New England Journal of Medicine. 2010;362(24):2282-94.

29. Jackson DJ, Chopra M, Doherty TM, et al. Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV-1. AIDS. 2007;21(4):509-515.

30. Stringer EM, Sinkala M, Stringer JSA, et al. Prevention of mother-to-child transmission of HIV in Africa: successes and challenges in scaling-up a nevirapine-based program in Lusaka, Zambia. AIDS. 2003;17(9):1377-82.

31.Colvin M, Chopra M, Doherty T, et al. Operational effectiveness of single-dose nevirapine in preventing mother-to-child transmission of HIV. Bulletin of the World Health Organization. 2007;85:466-472.

32. Ahmad N. Molecular mechanisms of HIV-1 mother-to-child transmission and infection in neonatal target cells. Life sciences. 2011;88(21-22):980-6.

33. Cao Y, Krogstad P, Korber BT, et al. Maternal HIV-1 viral load and vertical transmission of infection: the Ariel Project for the prevention of HIV transmission from mother to infant. Nature medicine. 1997;3(5):549-52.

34. McGowan JP, Shah SS. Prevention of perinatal HIV transmission during pregnancy. Journal of Antimicrobial Chemotherapy. 2000;46(5):657-68.

35. Muula AS. HIV Infection and AIDS Among Young Women in South Africa. Croatian medical journal. 2008;49(3):423-35.

36. Lopman B, Lewis J, Nyamukapa C, et al. HIV incidence and poverty in Manicaland, Zimbabwe: is HIV becoming a disease of the poor? AIDS. 2007;21 Suppl 7:S57-66.

37. Boer K, England K, Godfried MH, Thorne C. Mode of delivery in HIV-infected pregnant women and prevention of mother-to-child transmission: changing practices in Western Europe. HIV medicine. 2010;11(6):368-78.

38. Moodley D, Bobat RA, Coutsoudis A, Coovadia HM. Caesarean section and vertical transmission of HIV-1. Lancet. 1994;344(8918):338.

39. Stringer JSA, Sinkala M, Maclean CC, et al. Effectiveness of a city-wide program to prevent mother-to-child HIV transmission in Lusaka, Zambia. AIDS. 2005;19(12):1309-15.

PART D

Appendix

Tables

Table 1. Characteristics of mother/child pairs included in the study

Characteristic	N=874
Sex of child	
Male	465 (53.20%)
Female	409 (46.80)
HIV status of the mother	
Negative	777 (88.90)
Positive	97 (11.10)
Age of mother	
15-24 years	455 (52.18)
25-35 years	338 (38.76)
Greater than 35 years	79 (9.060) Missing data n = 2
Delivery status	
Caesarian-section	122 (14.02)
Normal vaginal delivery	748 (85.98) Missing data n = 4
Household has electricity	
Yes	813 (93.13)
No	60 (6.87) Missing data n = 1
Source of drinking water	
No tap water	29 (3.32)
Piped water in household	808 (92.45)
Public tap	37 (4.23)

Mother attended antenatal services at least once	
No	1 (0.11)
Yes	870 (99.89) Missing data n = 3
Mortality	
Living	777 (88.90)
Not living	97 (11.10)

Table 1.1 Characteristics of exposed children included in the study

Characteristic	N=97
HIV-exposed children (N=97) who received some form of PMTCT	
prophylaxis	N=97
No	22 (25.58)
Yes	64 (74.42) Missing data n = 11
HIV-positive mothers who received some form of PMTCT	
prophylaxis	N=97
No	19 (20.00)
Yes	76 (80.00) Missing data n =2
HIV transmission in HIV-exposed children	N=97
Negative	76 (78.35)
Positive	21 (21.65)

Table 2.1. Survival among children born to HIV-infected mothers stratified by exposure of the mother to some form of PMTCT, compared to unexposed

Variable	Not living	living	p value	OR
Mother received some form of PMTCT				
No	0 (0.00%)	19 (100%)	p=0.638	1.95
Yes	2 (2.63)	74 (97.37)		
Total	2	93		
HIV and PMTCT				
HIV exposed & NOT on PMTCT	0 (0.00%))	19 (100.00%)	p=1.000	
HIV exposed & ON PMTCT	2 (6.25)	74 (97.37)		0.52
Unexposed	30 (3.86)	747 (96.14)		8.52

- 2 children had missing information regarding PMTCT exposure from the mother

Table 2.2. HIV status of the child stratified by exposure of the mother to some form of PMTCT

Variable	Child HIV+	Child HIV -	pvalue	OR
Mother received some form of PMTCT				
No	10 (52.63).	9 (47.37)	P<0.001	8.27 (2.27-29.89)
Yes	9 (11.84)	67 (97.37)		

Table 3. Characteristics of mothers of children under 2 years of age stratified by child survival including mother's exposure to PMTCT in HIV-exposed children

Variable	Not living (n = 32)	Living (n = 842)	p-value
Education level attained			
Primary	5 (4.10%)	117 (95.90 %)	p=0.844
Secondary	27 (3.80)	683 (96.20)	
Tertiary	0 (0.00)	24 (100.00)	
Age of mother			
15-24 years	13 (2.86)	442 (97.14)	p=0.329
25-35 years	15 (4.44	323 (95.56)	
Over 35 years	4 (5.06)	75 (94.94)	
Type of delivery			
Caesarian section	26 (18.31)	116 (81.69)	p=0.433
Normal vaginal delivery	6 (0.82)	722 (99.18)	
HIV status of the mother			
Negative	30 (3.86)	747 (96.14)	P=0.567
Positive	2 (2.06)	95 (97.94)	
HIV-infected mother received some form of PMTCT prophylaxis (n=97)	**Not living (n = 2)**	**Living (n = 95)**	
No	0 (0.00%)	19 (100.00)	p=0.638
Yes	2 (2.63)	74 (97.37)	

Table 4. Characteristics of children under 2 years including exposure of the mother to PMTCT in HIV-exposed children stratified by survival.

Variable	Not living (n = 32)	Living(n = 842)	p value
Sex			
Male	19 (4.09%)	446 (95.91%)	p=0.476
Female	13 (3.18)	396 (96.82)	
HIV status of the child	Not living (n = 2)	Living (n = 95)	
Negative	1 (1.32)	75 (98.68)	p=0.547
Positive	1 (4.76)	20 (95.24)	
HIV-infected mother received some form of PMTCT prophylaxis (n = 97)			
No	0 (0.00)	19 (100)	p=0.587
Yes	2 (2.63)	(97.37)	

Table 5. Characteristics of mother and child associated with HIV transmission in HIV-exposed children

Characteristics	HIV- (N=76)	HIV+ (N=21)	Pvalue (crude)	Crude OR	Adjusted OR	p value (adjusted)
Sex of child						
Female	32 (82.05)	7(17.95)	p=0.469			p=0.409
Male	44(75.86)	14(24.14)		0.69(0.25;1.90)	2.67(0.26;27.44)	
Education level attained						
Primary	17(78.83)	7(29.17)	p=0.306			p=0.7.54
Secondary	59(80.82)	14(19.18)		0.58(0.20;1.66)	0.69(0.07;6.96)	
Age of mother						
15-24 years	16(66.67)	8(33.33)				
25-35 years	51(87.93)	7(12.07)	**p=0.029**	**0.27(0.09;0.88)**	0.76(0.09;6.22)	p=0.802
35 years	9(64.29)	5(35.71)	P=0.881	1.11(0.28;4.43)	0.21(0.003;24.36)	P=0.591
Mother received some						

form PMTCT						
No	9(47.37)	10(52.63)	**p<0.001**			p=0.290
Yes	67 (88.16)	9(11.84)		**0.12(0.04;0.38)**	0.16(0.01;4.83)	
Child received some form						
of PMTCT prophylaxis						
No	10 (45.45)	12 (54.55)				
Yes	56 (87.50)	8 (12.504)	**p<0.001**	**0.13(0.04;0.40)**	0.7(0.05;9.36)	p=0.789
Ever hospitalized child						
since birth						
No	66 (83.54)	13 (16.46)	p=0.013			p=0.047
Yes	10 (55.52)	8 (44.44)		4.06(1.35;12.25)	35.16(1.05;1177.15)	
Mode of delivery						
Natural vaginal delivery	62 (75.61)	20 (24.39)	p=0.180	4.19(0.52;34.09)	1.65(0.04;75.72)	p=0.796
Caesarean section	13 (92.86)	1 (7.14)				
Household electricity						
No	6 (85.71)	1 (14.29)	p=0.627			p=0.946
Yes	70 (77.78)	20 (22.22)		1.71(0.19;15.08)	1.16(0.01;93.13)	

Household Source of water						
No tap water	2 (33.33)	4 (66.67)	**p=0.017**			p=0.704
Piped water in household	74 (81.32)	17 (18.68)		**0.11(0.02;0.68)**	0.51(0.02;17.07)	
Child still breastfeeding at time of interview						
No	10 (62.50)	6 (37.50)	p=0.850			p=0.850
Yes	17 (65.38)	9 (34.62)		0.88(0.24;3.22)	2.89(0.23;37.06)	

Table 6. Characteristic of mother and child associated with survival in all children and in HIV-exposed children

Characteristics	Not living (32)	Living(842)	pvalue (adjusted)	Crude OR	Adjusted OR
Sex of child					
Female	13 (3.18)	396 (96.82)	p=0.742		
Male	19(4.09)	446 (95.91)		1.30(0.63;2.66)	1.15(0.5;2.62)
Education level attained					
Primary	5 (4.10)	117 (95.90)	p=0.844		
Secondary	27(3.80)	683 (96.20)		1.08(0.41;2.86)	*
Tertiary	0	24 (100)		1.00(0.00;0.00)	*
Age of mother					
15-24 years	13 (2.86)	442 (97.14)	p=0.742		

25-35 years	15 (4.44)	323 (95.56)		0.63(0.30;1.35)	0.86(0.3;2.12)
35 years	4 (5.06)	75 (94.94)		0.55(0.18;1.74)	0.55(0.16;1.91)
Ever hospitalized child since birth					
Yes	17 (2.23)	747 (97.77)	**p=0.006**	**0.24(0.10;0.54)**	**0.28(0.12;0.69)**
No	9 (8.82)	93 (91.18)			
Mode of delivery					
Normal vaginal delivery	26 (3.48)	722 (96.52)	p=0.551	1.44(0.58;3.57)	1.37(0.49;3.83)
Caesarean section	6 (4.92)	116 (95.08)			
Household electricity					
No	1 (1.67)	59 (98.33)	p=0.719		
Yes	31 (3.81)	782 (96.19)		0.43(0.06;3.19)	4.58(0.46;45.24)
Household Source of water					
No tap water	2 (3.03)	64(96.97)	p=0.547		

Piped water in household	30 (3.71)	778 (96.29)		0.81(0.19;3.7)	1.66(0.32;8.58)
Child still breastfeeding at time of interview					
No	9 (4.21)	205 (95.79)	**p=0.001**		
Yes	1 (0.18)	540 (99.82)		**23.71(2.98;188.30)**	**5.08(1.93;13.39)**
Mother received some form for PMTCT n = 95					
No	0	19 (100)	p=0.602		*
Yes	2 (2.63)	74 (97.37)		1.47(0.34;6.27)	0.58(0.07;4.59)
child received some form of PMTCT prophylaxis n = 86					
Yes	2 (9.09)	20 (90.91)	p=0.116	1.25(0.29;5.36)	*-
No	0	64 (100)			

*These variables were eliminated due to collinearity

Ethics approval letter

Letter of approval from the UCT Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room ES2-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 6501236 • Facsimile [021] 406 6411
Email:shahieda.amardien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 March 2015

HREC/REF: 271/2014

Prof D Coetzee
School of Public Health & Family Medicine
Falmouth Building
FHs

Dear Prof Coetzee

Project Title: PMTCT EFFECTIVENESS IN AFRICA: RESEARCH AND LINKAGES TO CARE (Mmed student Tembeka Sineke)

Thank you for your letter dated 24th February 2015, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has formally approved the above mentioned study.

Approval is granted for one year until the 30 March 2016.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

We acknowledge that the following students:-Tembeka Sineke is also involved in this project.

Please quote the HREC REF in all your correspondence.

Yours sincerely

Signed by candidate Signature Removed

PROFESSOR M BLOCKMA
CHAIRPERSON,HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.hstitutional Review Board (IRS) number: RB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), nternational Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines

The Research Ethics Committee granting this approval is in compliance with the CH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part SO, 56 and

Sample size calculation

Assuming:

- Difference between children exposed to PMTCT and unexposed = 20% (p),

- 95% confidence interval (equivalent to Z2), and

    - 5% precision (e):

n_0 = Z2 * p * (1-p) / e2

n_0 = (1.96)2 * (0.20) * (1-0.2) /(.05)2

n_0 = 245.8624

	House Number _____	Study Site Code _____		
NO	**QUESTIONS AND FILTERS**	**CATEGORIES**	**CODE**	**SKIP**
999	**SECTION 10. PREGNANCY CARE FOR EACH CHILD.** Now I would like to ask you some questions about the health of your children born in the last five years. We will talk about each child separately, starting with the most recent birth. This also includes any child that was born but passed away before it turned 2 years old in the last 2 years.			→1000
1000	1000. Record line number of [name] from the household listing.	Line number____		→1001
1001	1001. From HH listing Name living or not.	Living	1	→1002
		Not living	2	→1002
1002	1002. When was [name] born?	_____	Date	→1003
1003	1003. Are you [name's] biologic mother?	Yes	1	→1004
		No	2	→1100
1004	1004. When you were pregnant with [name], did you consult for antenatal care for this pregnancy?	Yes	1	→1005
		No	2	→1300
1005	1005. Is there any antenatal record or consultation book for [name] where his/her antenatal care is written down.	Yes	1	→1006
		No	2	→1007
1006	1006. May I see it? *(if reluctant response, encourage to view booklet)*	Yes	1	→1007
		No	2	
		I can not find booklet at the moment	3	
1007	1007. Where did you first receive antenatal care?	Home ("unbooked")	1	→1010
		Govt Hosp	2	→1008
		Govt Health Centre	3	
		Govt Health Post	4	
		Private sector Clinic	5	
		Mission Hospital	6	
		Mission Health Centre	7	
		Mission Health Post (primary health center)	8	
		Other	9	
1008	1008. Please tick source of information .	Only Recall	1	→1009
		Only Medical record	2	
		Medical record and Recall	3	
		Other	4	
1009	1009. Name of Health Facility *(fill out 'unknown' if not known)*	Name _____	Text	→1010

1010	1010. Please tick source of information.	Only Recall	1	→1011
		Only Medical record	2	
		Medical record and Recall	3	
		Other	4	
1011	1011. During [name's] pregnancy how many months pregnant were you when you first received antenatal care?	2 Months	1	→1012
		3 Months	2	
		4 Months	3	
		5 Months	4	
		6 Months	5	
		7 Months	6	
		8 Months	7	
		9 Months	8	
		Don't know	9	
1012	1012. Please tick source of information .	Only Recall	1	→1013
		Only Medical record	2	
		Medical record and Recall	3	
		Other	4	
1013	1013. During [Name's] pregnancy, were you tested for syphilis?	Yes	1	→1014
		No	2	
		Don't know	3	→1017
1014	1014. Please tick source of information .	Only Recall	1	→1015
		Only Medical record	2	
		Medical record and Recall	3	
		Other	4	
1015	1015. Were you told the result of your syphilis test?	Yes	1	→1016
		No	2	
1016	1016. Please tick source of information.	Only Recall	1	→1017
		Only Medical record	2	
		Medical record and Recall	3	
		Other	4	
1017	1017. During [name's] pregnancy what was the result of your syphilis test?	Positive	1	→1018
		Negative	2	
		Don't want to tell you	3	→1019
		Don't know	4	
1018	1018. Please tick source of information.	Only Recall	1	→1019
		Only Medical record	2	
		Medical record and Recall	3	
		Other	4	
1019	1019. Were you given an injection for treatment of syphilis?	Yes	1	→1020
		No	2	
		Don't know	3	

1020	1020. Please tick source of information.	Only Recall	1	→1021
		Only Medical record	2	
		Medical Record and Recall	3	
		Other	4	
1021	1021. During [name's] pregnancy were you tested for HIV?	Yes	1	→1022
		No	2	
		Don't know	3	→1025
		Don't want to tell you	4	→1100
1022	1022. Please tick source of information.	Only Recall	1	→1023
		Only Medical record	2	
		Medical Record and Recall	3	
		Other	4	
1023	1023. What was the result of this test?	HIV positive	1	→1024
		HIV negative	2	
		Don't know	3	→1025
		Don't want to tell you	4	→1200
1024	1024. Please tick source of information.	Only Recall	1	→1025
		Only Medical record	2	
		Medical Record and Recall	3	
		Other	4	
1025	1025. During (Name's) pregnancy, were you given any drugs to prevent mother to child transmission of HIV? *(show picture of Nevirapine and AZT)*	Yes	1	→1026
		No	2	
		No, I am already taking HAART	3	→1035
		No, I tested HIV negative	4	→1200
		Can not remember	5	
1026	1026. Please tick source of information.	Only Recall	1	→1027
		Only Medical record	2	
		Medical Record and Recall	3	
		Other	4	
1027	1027. What medications were you given? *(show pictures to help remember)*	NVP only	1	→1028
		AZT only	2	
		NVP and AZT	3	
		HAART (or local name)	4	→1035
		Can not remember	6	→1200
		Other	7	→1200
1028	1028. Please tick source of information.	Only Recall	1	→1029
		Only Medical record	2	
		Medical Record and Recall	3	
		Other	4	
1029	1029. Did you take the Nevirapine tablet?	Yes	1	→1030
		No	2	→1034
		Can not remember	3	→1032

1030	1030. When did you take the Nevirapine tablet?	When I went into labor	1	→1031
		After I delivered	2	
		1-7 days before delivery	3	
		Can not remember	4	→1034
1031	1031. How many times did you take the Nevirapine tab?	One time	1	→1034
		Two times	2	
		More than 2 times	3	
		Can not remember	4	
1032	1032. Did you take the AZT?	Yes	1	→1033
		No	2	→1200
		I was not given AZT tablets	3	
		Can not remember	4	
1033	1033. If you were given AZT, how many tablets did you take?	All of the tablets	1	→1034
		Some Of The Tablets	2	
		None of the tablets	3	→1200
		Can not remember	4	
1034	1034. During [Name's] pregnancy, when did you start taking the AZT tablets?	8 Weeks	1	→1200
		12 Weeks	2	
		16 Weeks	3	
		20 Weeks	4	
		24 Weeks	5	
		28 Weeks	6	
		32 Weeks	7	
		36 Weeks	8	
		38 Weeks	9	
		Can not remember	10	
1035	1035. When did you start taking HAART?	Before pregnancy	1	→1200
		During pregnancy	2	
		After delivery	3	
		Can not remember	4	
NO	**QUESTIONS AND FILTERS**	**CATEGORIES**	**CODE**	**SKIP**
1100	**SECTION 11:** QUESTIONS FOR CAREGIVER OTHER THAN MOTHER	Continue	1	→1101
		back to index	2	→31
1101	1101. What is reason that [name] is not staying with the mother?	Mother has passed away	1	→1102
		Mother lives elsewhere	2	→1102
1102	1102. Did the mother consult for antental care in this pregnancy?	Yes	1	→1103
		No	2	→1200
		Don't Know	3	→1200
1103	1103. Where did her first ANC visit take place? *(fill in 'unknown' if unknown)*	Place _____	text	→1104
1104	1104. Name of Health Facility	Name _____	text	→1105

1105	1105. How many months pregnant was she when she first received antenatal care?	1 Month	1	→1200
		2 Months	2	
		3 Months	3	
		4 Months	4	
		5 Months	5	
		6 Months	6	
		7 Months	7	
		8 Months	8	
		9 Months	9	
		Don't know	10	
NO	**QUESTIONS AND FILTERS**	**CATEGORIES**	**CODE**	**SKIP**
1200	**SECTION 12**: REVIEW OF ANTENATAL RECORD LAB TESTS *(for both living and dead mothers-if possible)*	Continue	1	→1201
		Back to index	2	→32
1201	1201. Do you have the ANC card from this pregancy? If so, can it be shown? *(verfiy Q 1202-1204)*	Yes, Seen	1	→1202
		Yes, Not Seen	2	→1300
		No Card	3	→1300
1202	1202. Maternal HIV antibody test	Pos	1	→1203
		Neg	2	
		Indeterminate	3	
		Not done	4	
		Nothing written on card	5	
1203	1203. Syphilis test result	Pos	1	→1204
		Neg	2	
		Not done	3	
		Nothing written on card	4	
1204	1204. Hemoglobin *(fill out '00' if unknown)*	Grams _____	text	→1300
NO	**QUESTIONS AND FILTERS**	**CATEGORIES**	**CODE**	
1300	**SECTION 13:** BIRTH HISTORY FOR EACH CHILD *(if biological mother has passed away ask a reliable family member)*	Continue	1	→1301
		Back to index	2	→33
1301	1301. Where did the birth of [name] take place?	Your Home	1	→1302
		Other Home	2	
		Govt Hospital	3	→1303
		Govt Health Clinic	4	
		Govt Health Post	5	
		Private Hospital/Clinic	6	
		Mission Hospital	7	
		Mission Health Clinic	8	
		Mission Health Post (primary health center)	9	
		Don't know	10	→1304

1302	1302. Was [name] taken to a health center after delivery within 3 days of birth?	Yes	1	→1303
		No	2	→1305
		Don't Know	3	
1303	1303. Name of Health Facility *(fill in 'unknown' if unknown)*	Name _____		→1304
1304	1304. Was [name] delivered by cesarean section	Yes	1	→1305
		No	2	
		Don't know	3	
1305	1305. Who assisted with the delivery of [name]?	HEALTH PROFESSIONAL:Doctor	1	→1306
		HEALTH PROFESSIONAL: Nurse/Midwife	2	
		HEALTH PROFESSIONAL : Unskilled Worker at Health Centre	3	
		Traditional/Trained Birth Attendant	5	
		Friend/neighbour	6	
		Family Member	7	
		No one	8	
		Other	9	
		Don't know	10	
1306	1306. Was [name] weighed at birth?	Yes	1	→1307
		No	2	→1308
		Don't know/not recorded	9	
1307	1307. How much did [name] weigh? (fill out '00' if unknown)	_____grams		→1308
1308	1308. Did [name] receive any Polio vaccination before discharge from the clinic or hospital?	Yes	1	→1309
		No	2	
		Do not remember/Do not know	3	
1309	1309. Did [name] receive any AZT syrup in his mouth before discharge from the clinic or hospital?	Yes	1	→1310
		No	2	
		Do not remember/Do not know	3	
		Not applicable (mother HIVneg)	4	→1312
1310	1310. Did [name] receive any Nevirapine syrup in his mouth before discharge from the clinic or hospital?	Yes	1	→1311
		No	2	
		Do not remember	3	
		Not applicable (mother HIVneg)	4	
1311	1311. Was [name] given Bactrim/Cozole to take every day beginning at 6 weeks even when [name] was not sick?	Yes	1	→ 1312
		No	2	
		Do not know	3	
1312	1312. Was [name] ever breastfed?	Yes	1	→1313
		No	2	→1315
1313	1313. Is [name] still breastfeeding? *(ONLY*	Yes	1	→1315

	ASK IF CHILD STILL LIVING)	No	2	→1314

1314	1314. For how many months was [name] breastfed?	1 Month	1	→1315
		2 Months	2	
		3 Months	3	
		4 Months	4	
		5 Months	5	
		6 Months	6	
		7 Months	7	
		8-10 Months	8	
		11-12 Months	9	
		13-18 Months	10	
		19-24 Months	11	
		Longer than 2 years	12	
1315	1315. How old was [name] when you first gave him/her water?	0-7 Days after birth	1	→1316
		2-4 Weeks after birth	2	
		1-2 Months after birth	3	
		3-4 Months after birth	4	
		5-6 Months after birth	5	
		More than 6 months after birth	6	
		Child was never given water	7	
		Do not remember	8	
1316	1316. Was [name] ever given formula? *(Note: formula is a specially prepared commercial product/food for babies like Pelargon/NAN/SMA)*	Yes	1	→1317
		No	2	→1319
		Do not know	9	
1317	1317. How old was [name] when formula was given for the first time? *(fill in 1/1/2010 if unknown)*	_____	Date	→1318
1318	1318. Why was [name] given formula feeding? *(circle all that apply) (Note: formula is a specially prepared commercial product/food for babies like Pelargon/NAN/SMA)*	Mother too sick to breast feed	1	→1319
		Mother died	2	
		Mother didn't have enough milk	3	
		[Name] was not staying with the mother	4	
		To prevent HIV transmission	5	
		Thought it was good for [name]	6	
		Mother had to go back to school/work	7	
		Other	8	
		Do not know/Do not remember	9	
1319	1319. Has [name] ever had tinned, powdered or fresh animal milk?	Yes	1	→1320
		No	2	→1322
		Do not know/Do not remember	3	

1320	1320. How old was [name] when milk such as tinned, powdered or fresh animal milk was given for the first time? *(fill in '1/1/2010' if unknown)*	_____	Date	→1321
1321	1321. Why was [name] given milk? *(circle all that apply)*	Mother too sick to feed	1	→1322
		Mother died	2	
		Mother did not produce enough milk	3	
		Baby was not staying with the mother	4	
		To prevent HIV transmission	5	
		Thought it was good for the child	6	
		Mother had to go back to school/work	7	
		Other	8	
		Do not know/Do not remember	9	
1322	1322. Has [name] ever been given tea, coffee or juice?	Yes	1	→1323
		No	2	→1324
		Do not know/Do not remember	3	
1323	1323. How old was [name] when tea, coffee or juice were given for the first time?	0-2 Months	1	→1324
		3-4 Months after birth	2	
		5-7 Months	3	
		8-10 Months	4	
		11-12 Months	5	
		More than 12 months	6	
		Can not remember	7	
1324	1324. Has [name] ever been given porridge or semi solid food?	Yes	1	→1325
		No	2	→1326
		Do not know/Do not remember	9	
1325	1325. How old was [name] when porridge or other semi solid food were given to him?	0-2 Months	1	→1326
		3-4 Months after birth	2	
		5-7 Months	3	
		8-10 Months	4	
		11-12 Months	5	
		More than 12 months	6	
		Can not remember	7	
1326	1326. Has [name] had family food? (solid food)	Yes	1	→1327
		No	2	→1328
		Do not know/Do not remember	3	

1327	1327. How old was [name] when family food (solid food) was given for the first time?	0-2 Months	1	→1328
		3-4 Months after birth	2	
		5-7 Months	3	
		8-10 Months	4	
		11-12 Months	5	
		More than 12 months	6	
		Can not remember	7	
1328	1328. What did [name] eat and drink yesterday? *(Mark all that apply)*	Breast milk	1	→1329
		Plain water	2	
		Formula milk	3	
		Animal milk	4	
		Porridge	5	
		Family food	6	
		Juice	7	
		Other	8	
1329	1329. Did anyone at the health facility instruct you on how to feed your infant after you were discharged or when you came for Post Natal Care?	Yes	1	→1330
		No	2	
1330	1330. Has [name] been tested for HIV?	Yes	1	→1331
		No	2	→1332
1331	1331. When was [name] tested for HIV? *(fill in '1/1/2010' if unknown)*	_____	Date	→1332
1332	1332. What was the result?	HIV Positive	1	→1333
		HIV negative	2	
		Indeterminant	3	
		Do not know	4	
		Do not want to tell you	5	
1333	1333. Has [name] ever spent the night in a clinic or hospital (AFTER being discharged from birth facility)?	Yes	1	→1334
		No	2	→1336
		Do not know/Do not remember	9	
1334	1334. How many times has [name] been hospitalized?	1 Time hospitalized	1	→1335
		2 Times hospitalized	2	
		3 Times hospitalized	3	
		4 Times hospitalized	4	
		More than 4 times hospitalized	5	
		Do not know	6	
1335	1335. What were the reasons for hospitalization?	Diarrhea	1	→1336
		Breathing problems	2	
		Fever	3	
		Vomiting	4	
		Other reason	5	
1336	1336. Did [name] sleep under a malaria net last night?	Yes	1	→1400
		No	2	

NO	QUESTIONS AND FILTERS	CATEGORIES	CODE	SKIP
1400	**SECTION 14:** CHILD HEALTH CARD	Continue	1	→1401
		Back to index	2	→34
1401	1401. Do you have an under 5 card where [name's] vaccinations are written down? If Yes, may I please see it?	Yes, Seen	1	→1402
		Yes, Not Seen	2	
		No Card	3	
1402	1402. BCG	Yes	1	→1403
		No	2	
1403	1403. Date BCG: *(fill out '1/1/2010' if unknown)*	Date: _____		→1404
1404	1404. OPV0	Yes	1	→1405
		No	2	
1405	1405. Date OPV0: *(fill out '1/1/2010' if unknown)*	Date: _____		→1406
1406	1406. OPV1	Yes	1	→1407
		No	2	
1407	1407. Date OPV1: *(fill out '1/1/2010' if unknown)*	Date: _____		→1408
1408	1408. OPV2	Yes	1	→1409
		No	2	
1409	1409. Date OPV2: *(fill out '1/1/2010' if unknown)*	Date: _____		→1410
1410	1410. OPV3	Yes	1	→14011
		No	2	
1411	1411. Date OPV3: *(fill out '1/1/2010' if unknown)*	Date: _____		→1412
1412	1412. DPT1	Yes	1	→14013
		No	2	
1413	1413. Date DTP1: *(fill out '1/1/2010' if unknown)*	Date: _____		→1414
1414	1414. DPT2	Yes	1	→1415
		No	2	
1415	1415. Date DTP2: *(fill out '1/1/2010' if unknown)*	Date: _____		→1416
1416	1416. DPT3	Yes	1	→1417
		No	2	
1417	1417. Date DTP3: *(fill out '1/1/2010' if unknown)*	Date: _____		→1418
1418	1418. Measles	Yes	1	→1419
		No	2	
1419	1419. Date Measles: *(fill out '1/1/2010' if unknown)*	Date: _____		→1420

1420	1420. Vitamin A	Yes	1	→1421
		No	2	
1421	1421. Date Vitamin A: *(fill out '1/1/2010' if unknown)*	Date: _____		→1422
1422	1422. IF CARD IS AVAILABLE: Is there an indication on [name's] card that the mother is HIV infected?	Yes	1	→1423
		No	2	
1423	1423. Is there any indication that [name] received PMTCT? *(Check all that apply)*	Mother's HIV status noted	1	→1414
		NVP given to mother	2	
		NVP given to [name]	3	
		AZT given to mother	4	
		AZT given to [name]	5	
		HAART given to mother	6	
		Other	7	
		No	8	
1424	1424. Is [name's] HIV test result on card?	Yes	1	→ 1425
		No	2	→ 1426
1425	1425. Is [name] HIV infected?	Yes	1	→ 1426
		No	2	
		Unknown, because [name] is not tested yet	3	
		Unknown	4	
1426	1426. Do you have more children below the age of 5 years living in this house? *(refer to children biological mother)*	Yes	1	→ 1000
		No	2	→ 1500

	House Number _____	Study Site Code _____		
NO	**QUESTIONS AND FILTERS**	**CATEGORIES**	**CODE**	**SKIP**
1500	1500. **SECTION 15** PHYSICAL EXAM/LAB TESTS. Enter Line number mother *(drop down list)*	Line number _____		→1501
1501	1501. Was Mother's Height (cm) (record to nearest 0.5 cm) recorded?	Yes, Height of the mother was recorded	1	→1502
		No, Height of the mother was not recorded	2	→1503
1502	1502. What was the Height of the mother?	Height in cm _____		→1504
1503	1503. The Height of the Mother was not collected. Reason:	Equipment did not work	1	→1504
		Equipment was not complete	2	
		Mother has physical handicap, which makes measurment not possible	3	
		Refusal during informed consent	4	
		Refused after informed consent was approved	5	
		Other	6	
1504	1504. Was Mother's Weight (kg) (record digital read out) collected?	Yes, Weight of the mother was recorded	1	→1505
		No, Weight of the mother was not recorded	2	→1506
1505	1505. What was the Weight of the mother?	Weight in kg _____		→1507
1506	1506. The Weight of the Mother was not collected. Reason:	Equipment did not work	1	→1507
		Equipment was not complete	2	
		Child has physical handicap, which makes measurment not possible	3	
		Refusal during informed consent	4	
		Refused after informed consent was approved	5	
		Other	6	
1507	1507. Was Mother's Blood Obtained?	Yes	1	→1509
		No	2	→1508
1508	1508. The blood sample was not collected from the mother. Reason:	Refusal during the Informed Consent	1	→1509
		Mother changed her mind after Informed Consent approval	2	
		Could not find a vein	3	
		Other	4	
1509	1509. This survey takes place in:	South Africa	1	→1511
		Zambia	2	
		Ivory Coast	3	
		Cameroon	4	→1510

1510	1510. Result Mother's HIV Test (for Cameroon only)	Positive	1	→1511
		Negative	2	
		Indeterminant	3	
		Not possible to do test, because could not be collected	4	
1511	1511. Was an Oraquick swab obtained from the mother?	Yes	1	→1512
		No, blood sample already collected	2	
		No, refusal during informed consent	3	
		No, refused after approval informed consent	4	
		No, test not done in country	5	
1512	1512. Enter line number Child	Line number _____		→1513
1513	1513. Was the Height of [Child Name's] recorded?	Yes, Height of the child was recorded	1	→1514
		No, Height of the child was not recorded	2	→1515
1514	1514. What was the Height of the child?	Height in cm: _____		→1516
1515	1515. The Height of [Child Name] was not recorded. Reason:	Equipment did not work	1	→1516
		Equipment was not complete	2	
		Child was so upset, it could not be measured properly	3	
		Child has physical handicap, which makes measurment not possible	4	
		Refusal during informed consent	5	
		Refused after informed consent was approved	6	
		Other	7	
1516	1516. Was the Weight of [Child Name] recorded? (in kg to nearest 0.1 kg)	Yes, the Weight of the child was recorded	1	→1517
		No, the Weight of the child was not recorded	2	→1518
1517	1517. What was the Weight of the child?	Weight in kg; _____		→1519
1518	1518. The Weight of [Child Name] was not recorded. Reason:	Equipment did not work	1	→1519
		Equipment was not complete	2	
		Child was so upset, it could not be measured properly	3	
		Child has physical handicap, which makes measurment not possible	4	
		Refused after informed consent was approved	5	
		Refused during informed consent	6	
		Other	7	

1519	1519. Was an antibody test performed on this child? *(circle all results that were obtained)* *(Cameroon only)*	Test not performed	1	→1520
		Determine Positive	2	
		Determine negative	3	
		Bioline HIV1 negative	4	
		Bioline HIV1 positive	5	
		Biolone HIV2 negative	6	
		Bioline HIV2 positive	7	
		Acon negative	8	
		Acon positive	9	
		Not appplicable/other country than Cameroon	10	
1520	1520. Was [Child Name's] Blood Obtained on a Dried Blood Spot Card?	Yes	1	→1522
		No	2	→1521
1521	1521. The Blood was not obtained on the Dried Blood Spot Card of [Child Name]. Reason:	Equipment did not work	1	→1522
		Equipment was not complete	2	
		Child was so upset, it could not be measured properly	3	
		Child has physical handicap, which makes measurment not possible	4	
		Refusal during informed consent	5	
		Refused after informed consent was approved	6	
		Other	7	
1522	1522. Was [Child Name's] Hemoglobin Result Obtained? *(only for interviewed children)*	Yes	1	→1523
		No	2	→1524
1523	1523. What was the result of the Hemoglobin test?	Result --.-- g/dl		→1525
1524	1524. The Hemoglobin result was not collected. Reason:	Equipment did not work	1	→1525
		Equipment was not complete	2	
		Child was so upset, it could not be measured properly	3	
		Child has physical handicap, which makes measurment not possible	4	
		Refused after informed consent was approved	5	
		Other	6	
1525	1525. Any other children from this biological mother, that are below 5 years and were interviewed in this questionnaire?	Yes	1	→1512
		No	2	→End

Journal submission guidelines

The Paediatric Infectious Diseases Journal

The Pediatric Infectious Disease Journal (PIDJ)

Online Submission and Review System

Author Resources

Instructions for Authors (this page)

Copyright Transfer & Disclosure (PDF)

Reprint Ordering

Permissions Requests

Reprints

SCOPE

The Pediatric Infectious Disease Journal is a peer-reviewed, multidisciplinary journal directed to physicians and other health care professionals who manage infectious diseases of childhood.

Ethical/Legal Considerations

A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the journal, its editors, or the publisher. All manuscripts must be submitted on-line through the journal's web site at http://pidj.edmgr.com/. See submission instructions under "Online manuscript submission."

Patient anonymity and informed consent: It is the author's responsibility to ensure that a patient's anonymity be carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Authors should mask patients' eyes or, if the eye area is the focus of the illustration, the patient's nose and mouth, and they should remove patients' names from figures unless written consent obtained from the patients is submitted with the manuscript.

Copyright: The corresponding author will complete the copyright questions within the submission steps, and provide each co-authors email address. The co-authors are emailed a hyperlink via which they will verify their co-authorship and complete the Copyright Transfer and Disclosure Form within EM. The co-authors are not required to register for an account in EM and no new accounts are created for them, rather, they are completing a form that is tied to the submission record.

Conflicts of interest: Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding:". For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker's bureau for Organization X − the CME organizers for Company A. For the remaining authors none were declared.

In addition, each author must complete and submit the journal's copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (www.icmje.org/update.html).

A copy of the form is made available to the submitting author within the Editorial Manager submission process. Co-authors will automatically receive an Email with instructions on completing the form upon submission.

Compliance with NIH and Other Research Funding Agency Accessibility Requirements
A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism.

Permissions: Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyrighted form elsewhere, along with complete details about the source. Any permissions fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of Lippincott Williams & Wilkins.

Preparation of Manuscript

Manuscripts that do not adhere to the following instructions are returned to the corresponding author for technical revision before undergoing peer review. Also, to streamline the review process, on reviewing newly submitted manuscripts, we will identify those that do not meet the mission of the journal, provide no new information or insights into management of infectious diseases or are of more local importance and better suited for a regional journal and return them immediately to the authors to allow them to submit their work elsewhere in a timely fashion.

New Article Types

Research Reports This section comprises manuscripts on all aspects of the molecular pathogenesis and immunologic mechanisms of bacterial, viral, fungal and other infections in infants, children and adolescents. The emphasis will be on manuscripts that present data that are clinically applicable and provide a more thorough understanding of the pathophysiologic basis of infections in children and that could impact eventual treatment and prevention. The manuscripts can be formatted as original studies or brief reports and will be peer reviewed.

HIV Reports The section comprises of high-quality, high-impact original articles and brief reports of epidemiologic, clinical, translational and implementation science studies pertaining to the prevention, treatment and outcomes of HIV infection in infants, children, and adolescents.

Vaccine Reports Articles that present data from Vaccine Phase II-IV studies will appear in this section. These manuscripts receive the same peer review as articles submitted as Original Studies. The universal open access fee for all accepted manuscripts in this category is: $2000.00 US, plus an additional per-page fee with 2 options: 1) $50 per page for print and online publication; or 2) $25 per page for online only publication. All articles in this series will be available online by free

access. For manuscripts in this category, authors should refer to the "Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies" published in Vaccine (2009, vol. 27; pp 2282-8) and use case definitions as developed by The Brighton Collaboration (www.brightoncollaboration.org) whenever possible.

ESPID Reviews and Reports (or purple pages) This section comprises invited concise reviews on all aspects of infections in infants, children and adolescents including bacterial, viral, fungal and parasitic infections. Reviews on prevention, diagnosis, therapeutic interventions and drugs as well as on teaching and conferences in pediatric infectious diseases are the focus of this section and will concentrate on novel findings, development and controversial issues.

Manuscript Submission

Online manuscript submission: All manuscripts must be submitted on-line through the new web site at http://pidj.edmgr.com/. First-time users: Please click the Register button from the menu above and enter the requested information. On successful registration, you will be sent an E-mail indicating your user name and password. Print a copy of this information for future reference. Note: If you have received an E-mail from us with an assigned user ID and password, or if you are a repeat user, do not register again. Just log in. Once you have an assigned ID and password, you do not have to re-register, even if your status changes (that is, author, reviewer, or editor). If you experience any problems, please contact Amy Newman, Journal Manager, at PIDJournal@outlook.com, Ph 830-865-1249, Fax 214-710-2175.

Authors: Please click the log-in- button from the menu at the top of the page and on the next screen log into the system as an Author. Submit your manuscript according to the author instructions. You will be able to track the progress of your manuscript through the system. If you experience any problems, please contact Amy Newman, Journal Manager, at PIDJournal@outlook.com, Ph 830-865-1249, Fax 214-710-2175. Requests for help and other questions will be addressed in the order received. To submit a completed manuscript, the following documents are required: Cover Letter, Title Page, Abstract, and Manuscript. Tables and figures are optional. Each portion of the manuscript must be submitted as separate documents (i.e. cover letter, title page, abstract, manuscript, tables and figures all saved as separate files). The text documents, cover letter, title page, abstract and manuscript are to be uploaded as Microsoft Word documents. Tables are to be created in Microsoft Word also. Excel tables will not load properly. All figures should be TIFF, EPS or PowerPoint files.

General format: Submit manuscripts in English. Double space all copy, including legends, footnotes, tables, and references. Use a common font such as Arial or Times Roman in size 12. Enumerate all pages of the manuscript, beginning with the Title Page as page 1, and follow in sequence to the abstract, manuscript and all other attachments. If you are unfamiliar with numbering, you can search HELP while in Microsoft Word, and it will show in detail how to number all pages.

Title page: **Title page must be submitted as a separate file**. Include on the title page: (a) complete manuscript title; (b) authors' full names, highest academic degrees, and affiliations; (c) name and address for correspondence, including Fax number, telephone number, and E-mail address; (d) address for reprints if different from that of corresponding author (indicate whether reprints are available); and (e) all sources of support, including pharmaceutical and industry support, that require acknowledgment; (f) list three to five key words for indexing; (g) an abbreviated title of 55 characters or less used for the cover of the journal; (h) a running head title

of 44 characters or less including spaces used for page headings on the pages in which your article is published.

The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

Structured abstract for Original Studies and Supplement Articles: Abstracts must be submitted as a separate file. Limit the abstract to 250 words. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. Use the following subheads: Background, Methods, Results, and Conclusions (others may be added as needed).

Unstructured abstract for Instructive Cases and Brief Reports: Abstract must be submitted as a separate file. Limit the abstract to 60 words. It must be factual and comprehensive. Limit the use of abbreviations and acronyms, and avoid general statements (e.g. "the significance of the results is discussed").

Brief Reports: Papers for this section should be no longer than 5-6 double-spaced typed manuscript pages (fewer than 1500 words), 10 references and 1 figure or table. Word count does not include Title Page or Unstructured Abstract.

Letters to the Editors: Letters to the Editors should pertain to articles published within the Pediatric Infectious Disease Journal or highlight important new clinical or laboratory insights. Text should contain 500 words or fewer and less than 5 references.

ESPID Reviews and Reports: ERR reviews should contain a maximum of 2000 words (including references) and include up to 10 references and 1 table or figure. There is no abstract. A maximum of four authors is allowed.

Original Studies: Papers for this section do not have a word, reference, table or figure limit.

Text: Organize the manuscript into four main headings, Introduction, Materials and Methods, Results, and Discussion. If a brand name is cited, supply the manufacturer's name and address (city and state/country).

Abbreviations: For a list of standard abbreviations, consult the *American Medical Association Manual of Style*, 9th edition, or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure. Abbreviations are allowed only if used three times or more in text.

References: The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in text in the order of appearance, including those references cited in tables and figure legends at the chronological citation of the tables and figures in text. Cite unpublished data, such as papers submitted but not yet accepted for publication or personal communications, in parentheses in the text. If there are more than six authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at**http://www.nlm.nih.gov/tsd/ serials/lji.html**. Sample references are given below.

Journal article
1. Trujillo M, Correa N, Olsen K, et al. Cefprozil concentrations in middle ear fluid. *Pediatr Infect Dis J*. 2000;19:268 −270.

Book chapter
2. Grose C. Bacterial myositis and pyomyositis. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1998:704 − 708.

Entire book
3. Nelson JD, Bradley JS. *Nelson's Pocket Book of Pediatric Antimicrobial Therapy*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.

Proceedings
4. Harrigan PR, Dong W, Weber AE, et al. Highly mutated RT and protease [Abstract I-115]. In: 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, September 24 to 27, 1998. Washington, DC: American Society for Microbiology; 1998.

Online journals
5. Friedman SA. Preeclampsia. Obstet Gynecol. [serial online]. January 1988;71:22−37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

World Wide Web
6. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS web site]. June 1, 1996. Available at: http://www.ama-assn.org/ special/hiv/ethics. Accessed June 26, 1997.

Figures:

A) Creating Digital Artwork

1. Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42
2. Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
3. Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital artwork:

- Artwork should be saved as TIFF, EPS, or MS Office (DOC, PPT, XLS) files. High resolution PDF files are also acceptable.
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.

Figure legends: Include legends for all figures. They should be brief and specific, and they should appear on a separate manuscript page after the references. Legends should be part of the manuscript file on the disk. Use scale markers in the image for electron micrographs, and indicate the type of stain used.

Color figures: The journal accepts for publication color figures that enhance an article. Authors who submit color figures receive an estimate of the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge.

Supplemental Digital Content

Supplemental Digital Content (SDC): Authors may submit SDC via Editorial Manager to LWW journals that enhance their article's text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. All SDC files should be uploaded as the author would like them presented in the final article. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are not copyedited by LWW staff, they will be presented digitally as submitted. For SDC documents, any labels or legends should be included in the original SDC file when submitted. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

SDC Call-outs

Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as "Supplemental Digital Content," include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

Example:

We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

List of Supplemental Digital Content

A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.

Example:

Supplemental Digital Content 1. wmv

SDC File Requirements

All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs,

authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

Tables: Create tables using the table creating and editing feature of your word processing software (e.g., Word, WordPerfect). Do not use Excel or comparable spreadsheet programs. Provide a separate document for each table. Cite tables consecutively in the text, and number them in that order. Key each on a separate sheet, and include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviation not already defined in the text). Do not embed tables within the body of the manuscript. They should be self-explanatory and should supplement, rather than duplicate, the material in the text. In each table, the genus of each genus-species must be written out at its first appearance.

Style: *Stedman's Medical Dictionary* (27th edition) and *Merriam Webster's Collegiate Dictionary* (10th edition) should be used as standard references. Refer to drugs and therapeutic agents by their accepted generic or chemical names, and do not abbreviate them. Use code numbers only when a generic name is not yet available. Capitalize the trade names of drugs and place them in parentheses after the generic names. To comply with trademark law, include the name and location (city and state/country) of the manufacturer of any drug, supply, or equipment mentioned in the manuscript. Use the metric system to express units of measure and degrees Celsius or degrees Fahrenheit consistently throughout the manuscript to express temperatures, and use SI units rather than conventional units. Abbreviate "liter" in such forms as "3 units/L" and "5 mL"; write out when used alone (10 liters; 0.5-liter gavage). See also Day RA, ed. How to Write and Publish a Scientific Paper. 5th ed. Phoenix, AZ: The Oryx Press, 1998.

Financial disclosure: In the cover letter, indicate all affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials of the research discussed in the manuscript (e.g. employment, consultancies, stock ownership). All such information will be held in confidence during the review process. Should the manuscript be accepted, the Chief Editors will discuss with the author the extent of disclosure appropriate for publication.

After Acceptance

Open access

LWW's hybrid open access option is offered to authors whose articles have been accepted for publication. With this choice, articles are made freely available online immediately upon publication. Authors may take advantage of the open access option at the point of acceptance to ensure that this choice has no influence on the peer review and acceptance process. These articles are subject to the journal's standard peer-review process and will be accepted or rejected based on their own merit.

Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. The article processing charge for *The Pediatric Infectious Disease Journal* is $3,100. The article processing charge for authors funded by the Research Councils UK (RCUK) is $3,900. The publication fee is charged on acceptance of the article and should be paid within 30 days by credit card by the author, funding agency or institution. Payment must be received in full for the article to be published open access.

Authors retain copyright: Authors retain their copyright for all articles they opt to publish open access. Authors grant LWW a license to publish the article and identify itself as the original publisher.

Creative Commons license: Articles opting for open access will be freely available to read, download and share from the time of publication. Articles are published under the terms of the Creative Commons License Attribution-NonCommerical No Derivative 3.0 which allows readers to disseminate and reuse the article, as well as share and reuse of the scientific material. It does not permit commercial exploitation or the creation of derivative works without specific permission. To view a copy of this license visit:http://creativecommons.org/licenses/by-nc-nd/3.0.

Compliance with NIH, RCUK and other research funding agency accessibility requirements: A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW identifies to the National Library of Medicine (NLM) articles that require deposit and transmits the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism. LWW ensures that authors can fully comply with the public access requirements of major funding bodies worldwide. Additionally, all authors who choose the open access option will have their final published article deposited into PubMed Central.

RCUK funded authors can choose to publish their paper as open access with the payment of an article process charge, or opt for their accepted manuscript to be deposited (green route) into PMC with an embargo.

With both the gold and green open access options, the author will continue to sign the Copyright Transfer Agreement (CTA) as it provides the mechanism for LWW to ensure that the author is fully compliant with the requirements. After signature of the CTA, the author will then sign a License to Publish where they will then own the copyright.

It is the responsibility of the author to inform the Editorial Office and/or LWW that they have RCUK funding. LWW will not be held responsible for retroactive deposits to PMC if the author has not completed the proper forms.

FAQ for open access: http://links.lww.com/LWW-ES/A48

Page proofs and corrections: Corresponding authors receive page proofs to check the copyedited and typeset article before publication. Portable document format (PDF) files of the typeset pages and support documents (e.g., reprint order form) are sent to the corresponding author by E-mail. Complete instructions are provided with the E-mail for downloading and printing the files and for faxing the corrected page proofs to the publisher. Those authors without an E-mail address receive traditional page proofs. It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style stand if they do not alter the authors' meaning. Only the most critical changes to the accuracy of the content are made. Changes that are stylistic or are a reworking of previously accepted material are disallowed. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Authors may be charged for alterations to the proofs beyond those required to correct errors or to answer queries. Proofs must be checked carefully and returned within 24 to 48 hours of receipt, as requested in the cover letter accompanying the page proofs.

Reprints: Authors receive a reprint order form with the page proofs that includes reprint costs. Reprint order forms should be returned to Author Reprint Department, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Reprints are normally shipped 6 to

8 weeks after publication of the issue in which the item appears. Contact the Author Reprint Department, Lippincott Williams & Wilkins, 351 W. Camden Street, Baltimore, MD 21201; Fax: 410-528-4434; E-mail: reprintsgroup@lww.com with any questions.

Permissions: For permission and/or rights to use content for which the copyright holder is LWW or the society, please go to the journal's website and after clicking on the relevant article, click on the "Request Permissions" link under the "Article Tools" box that appears on the right side of the page. Alternatively, send an e-mail to customercare@copyright.com.

For Translation Rights & Licensing queries, contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

For Special Projects and Reprints (U.S./Canada), contact Alan Moore, Director of Sales, Lippincott Williams & Wilkins, Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Phone: 215-521-8638. E-mail: alan.moore@wolterskluwer.com

For Special Projects and Reprints (non-U.S./Canada), contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

Publisher's contact: Send corrected page proofs, color letters, and any other related materials to Emily Weisenreder, Emily.Weisenreder@wolterskluwer.com, 410-528-4102 (phone), 443-451-8147 (fax), or mail to Emily Weisenreder, Wolters Kluwer Health, 351 W. Camden Street, Baltimore, MD 21201.

Manuscript Checklist (before submission)

- Cover letter
- Title page (including conflicts of interest statement)
- Abstract
- Each co-authors email address so they can verify their authorship
- Manuscript with figure legend if applicable
- References double-spaced in US National Library of Medicine style
- Corresponding author and E-mail address designated (in cover letter and on title page)
- Permission to reproduce copyrighted materials or signed patient consent forms
- Acknowledgments listed for grants and technical support
- High quality print of electronic art . Tables created using table software features
- Figures created/saved as TIFF, EPS, or PowerPoint files
- At least 3 suggested reviewers